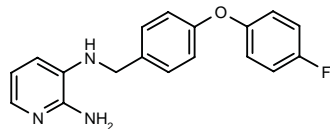


ANALGESIC AND ANESTHETIC
DRUGS

ANALGESIC DRUGS

311553

*N*³-[4-(4-Fluorophenoxy)benzyl]pyridine-2,3-diamine



C18 H16 F N3 O; Mol wt: 309.3424

ACTION – Sodium channel blocker with a *K_i* of 0.06 μM for inhibition of voltage-gated sodium currents in HEK-293 cells stably expressing the hSKM1 isoform of Na⁺ channels. Compound inhibited maximal electroshock (MES)-induced seizures with an ED₅₀ of 10 mg/kg i.v. in mice. Potentially useful for the treatment of seizures, neuropathic, surgical or chronic pain, as well as for the treatment and prevention of postischemic neuronal loss, neurodegenerative diseases and manic depression.

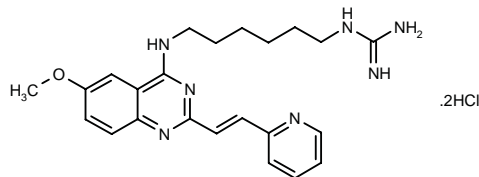
SOURCE – CoCensys.

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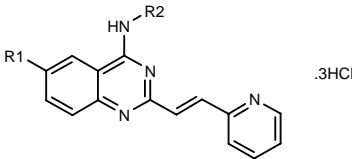
311598

N-[6-[6-Methoxy-2-[2-(2-pyridyl)vinyl]quinazolin-4-ylamino]hexyl]guanidine dihydrochloride



C23 H29 N7 O . 2HCl; Mol wt: 492.4519

ACTION – Nociceptin (N/OFQ) receptor modulator with *K_i* values of 0.003 and 0.019 μM against nociceptin and mu opioid receptors, respectively. In the acetic acid-induced writhing test in mice, compound demonstrated analgesic activity following administration into the spinal sub-arachnoid cavity (10 nmol/animal). Expected to be useful as an analgesic agent, for the treatment of migraine, chronic rheumatism and neuralgia, as well as for overcoming morphine resistance. Other exemplified heterocyclic compounds are:



Compound	R1	R2	Formula
311599	OMe	cis-4-[NH2C(=NH)NHCH2]-cyclohexyl	C ₂₄ H ₂₉ N ₇ O.3HCl
311601	Me	(CH2)6NHC(=NH)NH2	C ₂₃ H ₂₉ N ₇ .3HCl
311602	OMe	CH(Me)(CH2)5NHC(=NH)NH2	C ₂₄ H ₃₁ N ₇ O.3HCl

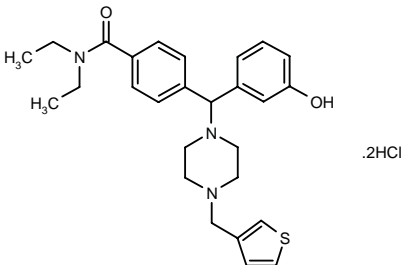
SOURCE – Nippon Shinyaku.

REFERENCES

1. Okano, M. and Mori, K. (Nippon Shinyaku Co., Ltd.) *Heterocycle derivs. and drugs*. WO 0172710.

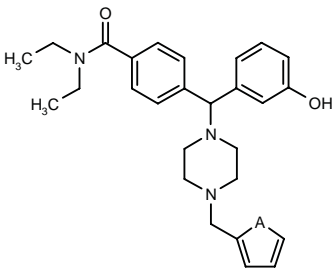
311690

N,N-Diethyl-4-[1-(3-hydroxyphenyl)-1-[4-(thien-3-ylmethyl)piperazin-1-yl]methyl]benzamide dihydrochloride



C27 H33 N3 O2 S . 2HCl; Mol wt: 536.5645

ACTION – Analgesic agent with delta opioid receptor-agonist properties. Other specifically claimed hydroxy-phenyl-piperazinyl-methyl-benzamide derivatives are:



Compound	A	Formula
311691	O	C ₂₇ H ₃₃ N ₃ O ₃
311692	S	C ₂₇ H ₃₃ N ₃ O ₂ S

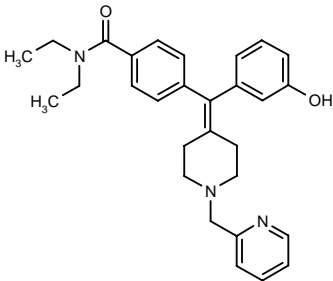
SOURCE – AstraZeneca.

REFERENCES

1. Brown, W. et al. (AstraZeneca AB) *Hydroxyphenyl-piperazinyl-methyl-benzamide derivs. for the treatment of pain.* WO 0174805.

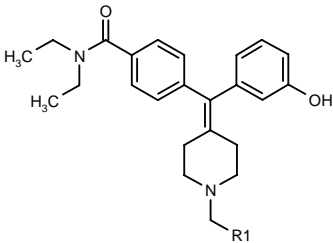
311693

N,N-Diethyl-4-[1-(3-hydroxyphenyl)-1-[1-(pyridin-2-ylmethyl)piperidin-4-ylidene]methyl]benzamide



C₂₉ H₃₃ N₃ O₂; Mol wt: 455.5987

ACTION – Analgesic agent with delta opioid receptor-agonist properties. Other specifically claimed hydroxyphenyl-piperidin-4-ylidene-methyl-benzamide derivatives are:



Compound	R1	Formula
311694	Ph	C ₃₀ H ₃₄ N ₂ O ₂
311695	2-thienyl	C ₂₈ H ₃₂ N ₂ O ₂ S
311696	3-thienyl	C ₂₈ H ₃₂ N ₂ O ₂ S
311697	2-furyl	C ₂₈ H ₃₂ N ₂ O ₃
311698	3-furyl	C ₂₈ H ₃₂ N ₂ O ₃
311699	4-Pyr	C ₂₉ H ₃₃ N ₃ O ₂
311700	2-imidazolyl	C ₂₇ H ₃₂ N ₄ O ₂
311702	4-imidazolyl	C ₂₇ H ₃₂ N ₄ O ₂
311704	2-thiazolyl	C ₂₇ H ₃₁ N ₃ O ₂ S

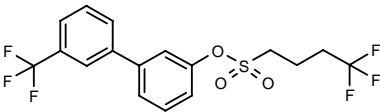
SOURCE – AstraZeneca.

REFERENCES

1. Brown, W. and Walpole, C. (AstraZeneca AB) *Hydroxyphenyl-piperidin-4-ylidene-methyl-benzamide derivs. for the treatment of pain.* WO 0174804.

311701

4,4,4-Trifluorobutane-1-sulfonic acid 3'-(trifluoromethyl)-biphenyl-3-yl ester



C₁₇ H₁₄ F₆ O₃ S; Mol wt: 412.3486

ACTION – Agent with agonist activity at cannabinoid CB₁ receptors and some activity at CB₂ receptors, potentially useful as an analgesic and for the treatment of neuro-degenerative diseases such as Parkinson’s disease. It demonstrated CB₁ receptor-agonist activity in the hypothermia assay in rats, giving an effective dose of 5 mg/kg p.o. for reducing body temperature by 1° centigrade. Its high metabolic stability and oral bioavailability make this compound suitable for oral administration.

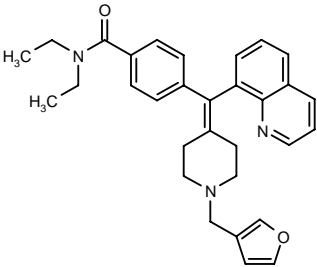
SOURCE – Bayer.

REFERENCES

1. Heil, M. et al. (Bayer AG) *Aryl and heteroaryl sulfonates.* DE 10015866, WO 0174763.

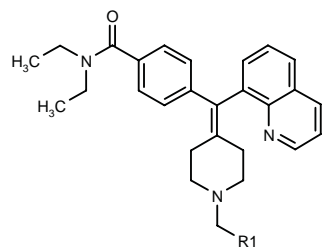
311705

N,N-Diethyl-4-[1-[1-(furan-3-ylmethyl)piperidin-4-ylidene]-1-(8-quinoliny)l)methyl]benzamide



C₃₁ H₃₃ N₃ O₂; Mol wt: 479.6207

ACTION – Analgesic agent with delta opioid receptor-agonist properties. Other specifically claimed quinolinyll-piperidin-4-ylidene-methyl-benzamide derivatives are:



Compound	R1	Formula
311706	Ph	C ₃₃ H ₃₅ N ₃ O
311707	2-furyl	C ₃₁ H ₃₃ N ₃ O ₂
311708	2-thienyl	C ₃₁ H ₃₃ N ₃ OS
311709	3-thienyl	C ₃₁ H ₃₃ N ₃ OS
311710	2-Pyr	C ₃₂ H ₃₄ N ₄ O
311711	2-imidazolyl	C ₃₀ H ₃₃ N ₅ O
311712	4-imidazolyl	C ₃₀ H ₃₃ N ₅ O
311713	4-Pyr	C ₃₂ H ₃₄ N ₄ O

SOURCE – AstraZeneca.

REFERENCES

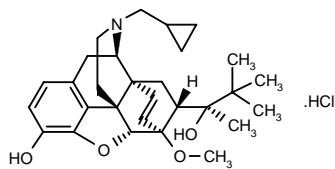
1. Brown, W. and Walpole, C. (AstraZeneca AB) *Quinoliny-piperidin-4-ylidene-methyl-benzamide derivs. for the treatment of pain.* WO 0174806.

HS-599

278204

(α S,5 α ,7 α)- α -*tert*-Butyl-17-(cyclopropylmethyl)-4,5-epoxy-3-hydroxy-6-methoxy- α -methyl-6,14-ethonorphinan-7-methanol hydrochloride

18,19-Dehydrobuprenorphine hydrochloride



C29 H39 N O4 . HCl; Mol wt: 502.0910

ACTION – Potent and long-acting opioid analgesic, a mu opioid receptor agonist with selectivity for mu over kappa and delta opioid receptors (K_i = 0.57, 8.5 and 32.0 nM, respectively); it showed partial agonist activity at mu opioid receptors *in vitro* (IC_{50} = 10.7 nM in guinea pig ileum) and antagonist activity at the other receptor subtypes. The analgesic activity of compound was 20-50 times higher than that of morphine and 2-fold higher than that of buprenorphine in the tail-flick test in mice and rats (ED_{50} = 0.14 and 0.04 mg/kg s.c., respectively), whereas it was much less active in the hot-plate test in mice, where it acted as a partial agonist. Moreover, compound showed little or no activity at the supraspinal level, indicating a low potential for dependence.

SOURCES – Universität Innsbruck, Innsbruck (AT); Università degli Studi “La Sapienza”, Rome (IT).

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1. Lattanzi, R. et al. *HS-599: A novel long acting opioid analgesic does not induce place-preference in rats.* Br J Pharmacol 2001, 134(2): 441.

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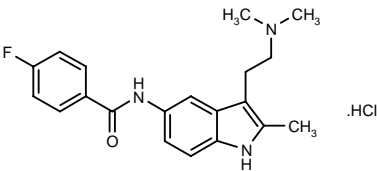
3. Schutz, J. et al. *Synthesis and pharmacological evaluation of 18,19-dehydrobuprenorphine.* Heterocycles 2001, 54(2): 989.

ANTIMIGRAINE DRUGS

LY-349950

311367

N-[3-[2-(Dimethylamino)ethyl]-2-methyl-1*H*-indol-5-yl]-4-fluorobenzamide hydrochloride



C20 H22 F N3 O . HCl; Mol wt: 375.8727

ACTION – Potent and selective 5-HT_{1F} receptor agonist with nanomolar affinity for human 5-HT_{1F} receptors (K_i = 8.2 nM), more than 100-fold selectivity over a panel of other receptors including 5-HT_{1B} and 5-HT_{1D} receptors, and 5-HT_{1F} receptor-agonist activity in cell lines expressing human receptors (EC_{50} = 6 nM; E_{max} = 98%). Compound strongly inhibited neurogenic dural inflammation in guinea pigs with ID_{50} values of 1.4 ng/kg i.v. and 4.3 ng/kg p.o., compared with ID_{50} values of 15 ng/kg i.v. and 4600 ng/kg p.o. for sumatriptan. When compound was given at the oral ID_{100} , it showed full efficacy by 1 h after administration and partial efficacy up to 24 h after dosing. No vasoconstriction was found in rabbit saphenous vein, indicating that it may lack the cardiovascular side effects of sumatriptan. Potentially useful for the treatment of migraine.

SOURCES – Lilly; Synaptic.

REFERENCES

1. Fritz, J.E. et al. (Eli Lilly and Company) *N-[2-Substd.-3-(2-aminoethyl)-1H-indol-5-yl]-amides: New 5-HT_{1F} agonists.* EP 0768301, JP 1999513666, WO 9713512.

2. Johnson, K.W. and Phebus, L.A. (Eli Lilly and Company) *Use of a serotonin 5-HT_{1F} agonist in the manufacture of a medicament for treating or ameliorating the symptoms of common cold or allergic rhinitis.* EP 0824917, US 5962473, WO 9806402.

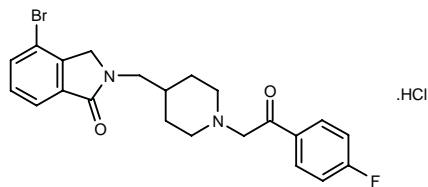
3. Xu, Y.-C. et al. *N-[3-(2-Dimethylaminoethyl)-2-methyl-1-H-indol-5-yl]-4-fluorobenzamide: A potent, selective, and orally active 5-HT_{1F} receptor agonist potentially useful for migraine therapy.* J Med Chem 2001, 44(24): 4031.

PSYCHOPHARMACOLOGIC DRUGS

ANXIOLYTICS

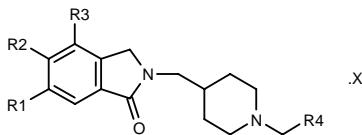
310395

4-Bromo-2-[1-[2-(4-fluorophenyl)-2-oxoethyl]piperidin-4-ylmethyl]isoindolin-1-one hydrochloride

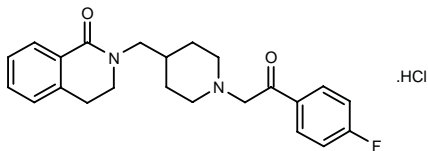


C22 H22 Br F N2 O2 . HCl; Mol wt: 481.7907

ACTION – Agent with affinity for σ -receptors ($K_i = 2.8$ nM in rat liver membranes), potentially useful for the treatment of CNS disorders such as anxiety, depression, schizophrenia, drug abuse, pain, motor dysfunction, cerebrovascular disorders, epilepsy, Alzheimer’s disease, Parkinson’s disease, cerebral tumors and attention deficit disorders, as well as for the treatment of irritable bowel syndrome, mucosal colitis, inflammatory bowel disease, hypertension, arrhythmia and angina pectoris. Other exemplified cyclic amide derivatives are:



Compound	R1	R2	R3	R4	X	Formula
310396	Br	H	H	4-F-PhCO	HCl	C ₂₂ H ₂₂ BrFN ₂ O ₂ .HCl
310397	H	H	F	4-F-PhCO	HCl	C ₂₂ H ₂₂ F ₂ N ₂ O ₂ .HCl
310399	H	Cl	H	4-F-PhCO	HCl	C ₂₂ H ₂₂ ClFN ₂ O ₂ .HCl
310401	H	OMe	H	4-F-PhCO	HCl	C ₂₃ H ₂₅ FN ₂ O ₃ .HCl
310403	H	H	H	COPh	HCl	C ₂₂ H ₂₄ N ₂ O ₂ .HCl
310404	H	H	H	4-F-PhOCH ₂	HCl	C ₂₂ H ₂₅ FN ₂ O ₂ .HCl
310405	H	H	H	cyclohexyl-CO	fumarate	C ₂₂ H ₃₀ N ₂ O ₂ .C ₄ H ₄ O ₄



310406: C23 H25 F N2 O2 . HCl

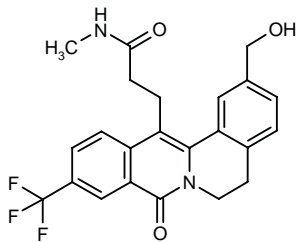
SOURCE – Mitsubishi Pharma.

REFERENCES

1. Yamabe, H. et al. (Mitsubishi Pharma Corp.) *Novel cyclic amide derivs.* WO 0164670.

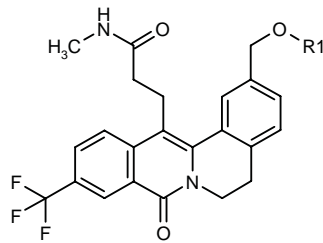
310530

3-[2-(Hydroxymethyl)-8-oxo-10-(trifluoromethyl)-6,8-dihydro-5*H*-dibenzo[*a,g*]quinolizin-13-yl]-*N*-methylpropionamide



C23 H21 F3 N2 O3; Mol wt: 430.4239

ACTION – Agent with affinity for the benzodiazepine (ω) site of the GABA_A receptor that acts as a selective agonist at the $\alpha 2$ and/or $\alpha 3$ subunits. Potentially useful for the treatment of anxiety, epilepsy and muscular spasms. Other exemplified dibenzo[*a,g*]quinolizine derivatives are:



Compound	R1	Formula
310532	Me	C ₂₄ H ₂₃ F ₃ N ₂ O ₃
310533	Pr	C ₂₆ H ₂₇ F ₃ N ₂ O ₃
310534	CON(Me) ₂	C ₂₆ H ₂₆ F ₃ N ₃ O ₄
310535	4-morpholinyl-CO	C ₂₈ H ₂₈ F ₃ N ₃ O ₅

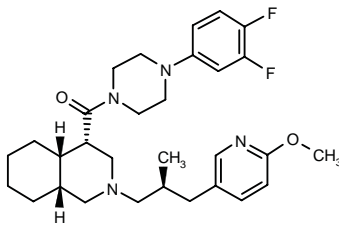
SOURCE – Sanofi-Synthélabo.

REFERENCES

1. Dachary, E. et al. (Sanofi-Synthélabo) *8-Oxo-5,8-dihydro-6H-dibenzo[a,g]-quinolizine-13-propanoic acid derivs., preparation and therapeutic use thereof.* WO 0170739.

310826

1-[4-(3,4-Difluorophenyl)piperazin-1-yl]-1-[(4*S*,4*aS*,8*aR*)-2-[3-(6-methoxypyridin-3-yl)-2(*S*)-methylpropyl]-perhydroisoquinolin-4-yl]methanone



C30 H40 F2 N4 O2; Mol wt: 526.6680

ACTION – Somatostatin sst₃ receptor antagonist, potentially useful in the treatment of anxiety, schizophrenia, depression and bipolar disorders. This compound increased exploratory behavior in mice at 0.3, 1 and 3 mg/kg p.o. and was active in a model of stress-induced hypothermia in mice at doses of 0.3-10 mg/kg p.o.

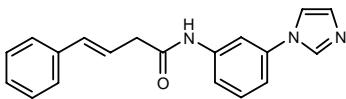
SOURCE – Novartis.

REFERENCES

1. Troxler, T.J. (Novartis AG;Novartis-Erfindungen VmbH) *Decahydro-isoquinolines*. WO 0170731.

310929

N-[3-(1*H*-Imidazol-1-yl)phenyl]-4-phenyl-3(*E*)-butenamide



C19 H17 N3 O; Mol wt: 303.3633

ACTION – 5-HT_{2C} receptor antagonist found to inhibit [³H]-mesulergine binding to 5-HT_{2C} receptors in rat prefrontal cortex preparations by 82% at 1 μM. Potentially useful for the treatment of CNS disorders including anxiety, depression, obsessive–compulsive neurosis, migraine, anorexia, Alzheimer’s disease, sleep disorders, polyphagia, panic, withdrawal from drug abuse, schizophrenia, and head and spinal cord injury.

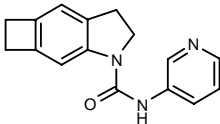
SOURCE – Fujisawa.

REFERENCES

1. Yamada, A. et al. (Fujisawa Pharmaceutical Co., Ltd.) *Novel amide cpds*. WO 0168585.

311047

N-(3-Pyridyl)-2,3,5,6-tetrahydro-1*H*-cyclobuta[*f*]indole-1-carboxamide



C16 H15 N3 O; Mol wt: 265.3145

ACTION – A representative compound within a series of cyclobutaindole carboxamides, potentially useful for the treatment of CNS disorders, particularly anxiety, panic attacks, obsessive–compulsive disorders, phobias, impulsive disorders, drug abuse, cognition disorders, psychoses, depression and mood disorders. Compound gave a minimum effective dose (MED) of 2.5 mg/kg s.c. in the Vogel conflict test in rats and the elevated plus-maze model in mice.

SOURCE – ADIR.

REFERENCES

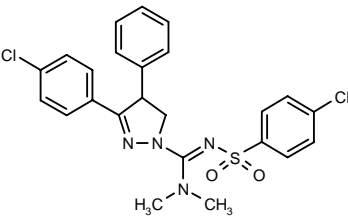
1. Peglioni, J.-L. et al. (ADIR et Cie.) *CNS active cyclobuta-indole carboxamide derivs., processes for their preparation and pharmaceutical compsns. containing them*. EP 1146044, FR 2807754, JP 2001302661.

ANTIPSYCHOTIC DRUGS

310627

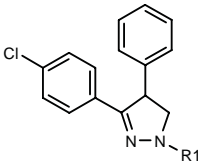
4-Chloro-*N*-[1-[3-(4-chlorophenyl)-4-phenyl-4,5-dihydro-1*H*-pyrazol-1-yl]-1-(dimethylamino)methylidene]-benzenesulfonamide

3-(4-Chlorophenyl)-*N*²-(4-chlorophenylsulfonyl)-*N*¹,*N*¹-dimethyl-4-phenyl-4,5-dihydro-1*H*-pyrazole-1-carbox-amidine



C24 H22 Cl2 N4 O2 S; Mol wt: 501.4358

ACTION – Cannabinoid CB₁ receptor antagonist, potentially useful in the treatment of psychiatric disorders including psychosis, anxiety, depression, attention deficits, eating disorders and obesity, as well as neurological disorders such as Parkinson’s disease, dementia, dystonia, Alzheimer’s disease, epilepsy, Huntington’s disease, Tourette’s syndrome, ischemia and pain. The use of this compound in the treatment of gastrointestinal and cardiovascular disorders is also reported. Other exemplified 4,5-dihydro-1*H*-pyrazole derivatives are:



Compound	R1	Formula
310628	3-CF3-PhCON=C(NHMe)	C ₂₅ H ₂₀ ClF ₃ N ₄ O
310629	4-Cl-PhSO ₂ N=C(NHMe)	C ₂₃ H ₂₀ Cl ₂ N ₄ O ₂ S
310630	3-CF3-PhSO ₂ NHCH ₂ CH ₂	C ₂₄ H ₂₁ ClF ₃ N ₃ O ₂ S

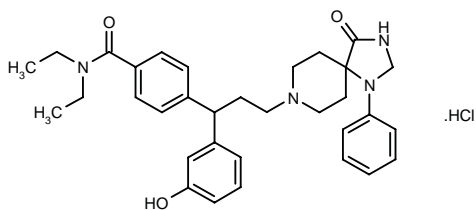
SOURCE – Solvay.

REFERENCES

1. Lange, J.H.M. et al. (Solvay Pharmaceuticals BV) *4,5-Dihydro-1H-pyrazole derivs. having CB 1-antagonistic activity*. WO 0170700.

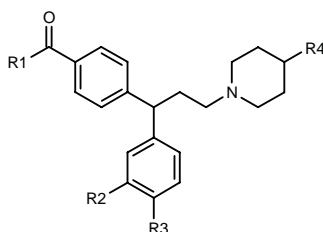
311187

N,N-Diethyl-4-[1-(3-hydroxyphenyl)-3-(4-oxo-1-phenyl-1,3,8-triazaspiro[4.5]dec-8-yl)propyl]benzamide hydrochloride

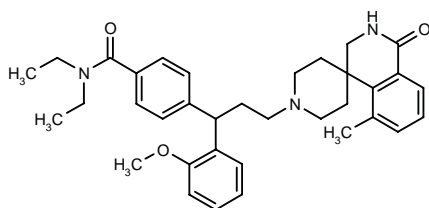


C33 H40 N4 O3 . HCl; Mol wt: 577.1649

ACTION – Delta opioid receptor agonist, as demonstrated by inhibition of [³H]-naltrindole binding to delta opioid receptors in rat brain with a K_i of 171 nM. Potentially useful for the treatment of CNS disorders such as schizophrenia, depression, stroke, epilepsy, Alzheimer's disease and Parkinson's disease, as well as peripheral nervous system disorders including pain. Other exemplified phenylalkylamine compounds are:



Compound	R1	R2	R3	R4	Formula
311188	N(Et)2	OMe	H	2-(CH2OH)-1-benzimidazolyl	C ₃₄ H ₄₂ N ₄ O ₃
311191	N(Et)2	F	H	2-oxo-2,3-dihydro-1-benzimidazolyl	C ₃₂ H ₃₇ FN ₄ O ₂
311192	N(Et)2	-OCH2O-	H	2-oxo-2,3-dihydro-1-benzimidazolyl	C ₃₃ H ₃₈ N ₄ O ₄
311193	1-Pip	OMe	H	2-oxo-2,3-dihydro-1-benzimidazolyl	C ₃₄ H ₄₀ N ₄ O ₃



311189: C35 H43 N3 O3

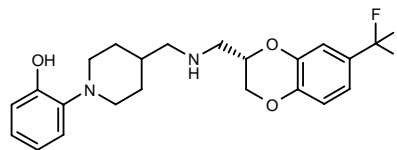
SOURCE – Meiji Seika.

REFERENCES

1. Tsushima, M. et al. (Meiji Seika Kaisha, Ltd.) *Diphenylalkylamine derivs. useful as opioid δ receptor agonists*. WO 0170689.

311479

(-)-2-[4-[7-(Trifluoromethyl)-2,3-dihydro-1,4-benzodioxin-2(S)-ylmethylaminomethyl]piperidin-1-yl]phenol



C22 H25 F3 N2 O3; Mol wt: 422.4445

ACTION – Agent with affinity for 5-HT_{1A} receptors, dopamine D2 receptors and/or α₁-adrenoceptors with K_i values of 37, 25 and 573 nM, respectively, in rat brain preparations. *In vivo*, compound gave an ED₅₀ of 0.6 mg/kg in the apomorphine-induced climbing test following oral administration to mice. Potentially useful particularly for the treatment of schizophrenia and anxiety. Further applications include depression, tardive dyskinesia, Parkinson's disease, obesity, hypertension, Tourette's syndrome, sexual dysfunction, drug abuse, Alzheimer's disease, obsessive-compulsive disorders, panic attacks, anorexia, migraine, non-insulin-dependent diabetes mellitus, constipation and arrhythmia.

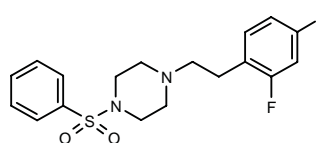
SOURCE – Knoll (Abbott).

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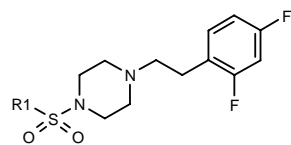
311573

1-[2-(2,4-Difluorophenyl)ethyl]-4-(phenylsulfonyl)piperazine



C18 H20 F2 N2 O2 S; Mol wt: 366.4300

ACTION – A selective 5-HT_{2A} antagonist, potentially useful for the treatment of schizophrenia, as well as other 5-HT_{2A}-mediated conditions such as depression, panic, obsessive-compulsive disorders, pain, sleep and eating disorders and drug abuse. Other specifically claimed phenylsulfonyl-substituted piperazines are:



Compound	R1	Formula
311574	4-Me-Ph	C ₁₉ H ₂₂ F ₂ N ₂ O ₂ S
311575	2,4,6-(Me)3-Ph	C ₂₁ H ₂₆ F ₂ N ₂ O ₂ S
311576	4-(AcNH)-Ph	C ₂₀ H ₂₃ F ₂ N ₃ O ₃ S
311577	2-Cl-Ph	C ₁₈ H ₁₉ ClF ₂ N ₂ O ₂ S
311578	2-CF3-Ph	C ₁₉ H ₁₉ F ₃ N ₂ O ₂ S
311579	2,6-(Cl)2-Ph	C ₁₈ H ₁₈ Cl ₂ F ₂ N ₂ O ₂ S
311580	2-(CF3O)-Ph	C ₁₉ H ₁₉ F ₃ N ₂ O ₃ S
311581	3-F-Ph	C ₁₈ H ₁₉ F ₃ N ₂ O ₂ S
311582	2-Cl-6-Me-Ph	C ₁₉ H ₂₁ ClF ₂ N ₂ O ₂ S
311584	3-Cl-2-Me-Ph	C ₁₉ H ₂₁ ClF ₂ N ₂ O ₂ S
311585	2-CN-Ph	C ₁₉ H ₁₉ F ₂ N ₃ O ₂ S
311586	2-Naph	C ₂₂ H ₂₂ F ₂ N ₂ O ₂ S
311588	1-Naph	C ₂₂ H ₂₂ F ₂ N ₂ O ₂ S

SOURCE – Merck Sharp & Dohme.

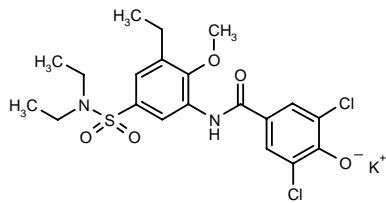
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TREATMENT OF MOOD DISORDERS

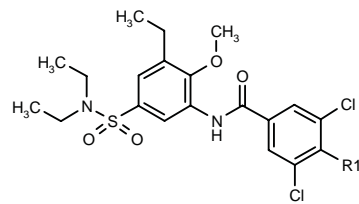
310686

3,5-Dichloro-*N*-[5-(*N,N*-diethylsulfamoyl)-3-ethyl-2-methoxyphenyl]-4-hydroxybenzamide potassium salt



C20 H23 Cl2 K N2 O5 S; Mol wt: 513.4807

ACTION – Agent with antagonist activity at corticotropin-releasing factor CRF₁ receptors (IC₅₀ = 263 nM), shown to inhibit CRF-induced adrenocorticotropin (ACTH) and corticosterone secretion in a mouse stress model. Potentially useful for the treatment of CRF-related disorders such as depression, anxiety, Alzheimer’s disease, Parkinson’s disease, Huntington’s chorea, eating disorders, etc. Other exemplified benzamide derivatives include the following:



Compound	R1	Formula
310687	ONa	C ₂₀ H ₂₃ Cl ₂ N ₂ NaO ₅ S
310688	OPO3H2	C ₂₀ H ₂₅ Cl ₂ N ₂ O ₆ PS

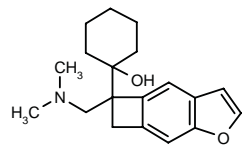
SOURCE – Japan Tobacco.

REFERENCES

1. Sato, M. et al. (Japan Tobacco Inc.) *Benzamide deriv. and use thereof*. WO 0162718.

311058

1-[5-(Dimethylaminomethyl)-5,6-dihydrocyclobuta[*f*]-benzofuran-5-yl]cyclohexanol



C19 H25 N O2; Mol wt: 299.4115

ACTION – A representative compound from a series of condensed cyclobutane-containing compounds that inhibits the reuptake of 5-HT, noradrenaline and dopamine, as demonstrated by an increase of 250, 500 and 400%, respectively, in the levels of 5-HT, noradrenaline and dopamine following s.c. administration to rats at 10 mg/kg. In the mouse elevated plus-maze test, it showed an ID₅₀ of 0.6 mg/kg s.c., indicating anti-depressant/antiimpulsive properties; fluoxetine in the same test gave an ID₅₀ of 8.03 mg/kg. Potentially useful in the treatment of depression, panic attacks, obsessive–compulsive disorders, phobias, impulsive disorders, drug abuse, anxiety, obesity and bulimia.

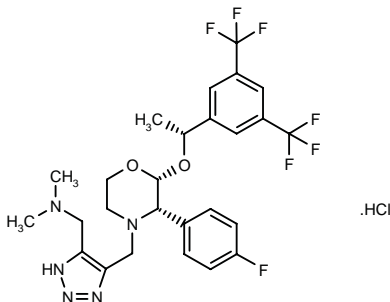
SOURCE – ADIR.

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1. Peglion, J.-L. et al. (ADIR et Cie.) *Derivs. of heterocycloalkylbenzocyclobutane and heteroarylbenzocyclobutane and their use as inhibitors of the recapture of serotonin and noradrenaline*. EP 1146041, FR 2807753, JP 2001302599.

311371

N-[4-[2(*R*)-[1(*R*)-[3,5-Bis(trifluoromethyl)phenyl]ethoxy]-3(*S*)-(4-fluorophenyl)morpholin-4-ylmethyl]-1*H*-1,2,3-triazol-5-ylmethyl]-*N,N*-dimethylamine hydrochloride



C26 H28 F7 N5 O2 . HCl; Mol wt: 611.9871

ACTION – Orally active and water-soluble NK₁ receptor antagonist (IC₅₀ = 0.19 nM for human NK₁ receptor) with over 3,000-fold selectivity over human NK₂ and NK₃ receptors and a panel of 100 other receptors, ion channels and enzymes. Compound was shown to inhibit GR-73632-induced foot tapping in gerbils (ID₅₀ = 0.2 and 0.3 mg/kg i.v., respectively, immediately after treatment and after 24-h pretreatment) and also showed antiemetic and potential antidepressant activity. In ferrets it inhibited cisplatin-induced emesis in a dose-dependent manner (ID₉₀ = 0.1 mg/kg i.v., 1.0 mg/kg p.o.), and in guinea pigs dose-dependent inhibition of neonatal vocalization was seen (ID₅₀ = 0.2 mg/kg p.o.). Potentially useful as an antiemetic agent and antidepressant.

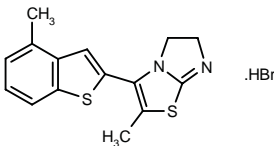
SOURCE – Merck & Co.

REFERENCES

1. Crocker, L. et al. (Merck & Co., Inc.) *Polymorphic form of a tachykinin receptor antagonist*. WO 0132656.
2. Harrison, T. et al. *An orally active, water-soluble neurokinin-1 receptor antagonist suitable for both intravenous and oral clinical administration*. J Med Chem 2001, 44(24): 4296.

310391

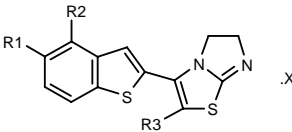
2-Methyl-3-(4-methyl-1-benzothien-2-yl)-5,6-dihydroimidazo[2,1-*b*]thiazole hydrobromide



C15 H14 N2 S2 . HBr; Mol wt: 367.3335

ACTION – Agent with the ability to inhibit the neuronal reuptake of 5-HT and noradrenaline (NA) and with affinity for 5-HT_{1A} receptors. This compound inhibited the binding of [³H]-8-OH-DPAT to 5-HT_{1A} receptors in rat hippocampal tissue by 97% at 1 μM; at the same concentration, it displaced [³H]-citalopram and [³H]-nisoxetine binding from 5-HT and NA binding sites in rat frontal cortical tissue by 93 and 83%, respectively, while showing no affinity for muscarinic receptors. Potentially useful for the treatment of depression, anxiety, schizophrenia, tardive dyskinesia, obesity, drug abuse, cognitive disorders including

Alzheimer's disease, cerebral ischemia, obsessive-compulsive disorders, panic, social phobias, bulimia, anorexia, type 2 diabetes, hyperglycemia and hyperlipidemia, stress and smoking cessation. Further applications include the treatment and prevention of metabolic diseases, sexual dysfunction, sleep apnea, premenstrual syndrome, urinary incontinence, etc., as well as the prevention of cardiovascular diseases, reduction of platelet adhesion and aiding in weight loss after pregnancy or smoking cessation. Other exemplified 1-benzothiazole-containing compounds include the following:



Compound	R1	R2	R3	X	Formula
310392	H	Cl	H	HBr	C ₁₃ H ₉ ClN ₂ S ₂ ·HBr
310393	H	Cl	CH ₂ OH		C ₁₄ H ₁₁ ClN ₂ OS ₂
310394	F	H	CH ₃	HBr	C ₁₄ H ₁₃ FN ₂ S ₂ ·HBr

SOURCE – Knoll (Abbott).

REFERENCES

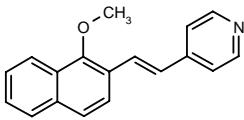
1. Doyle, K.J. et al. (Knoll AG) *Dihydroimidazol[2,1-b]thiazole and dihydro-5H-thiazolo[3,2-a]pyrimidines as antidepressant agents*. WO 0168653.

NEUROLOGIC DRUGS

ANTIEPILEPTIC DRUGS

311325

4-[2-(1-Methoxynaphthalen-2-yl)vinyl]pyridine

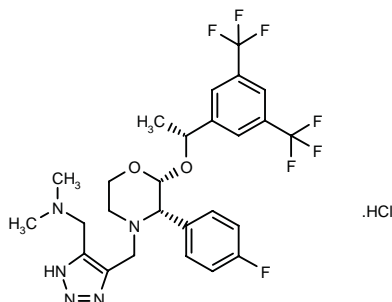


C18 H15 N O; Mol wt: 261.3225

ACTION – Ionotropic glutamate receptor antagonist that acts at the low-affinity GluR6 kainate receptor. Potentially useful for the treatment of a variety of neurological disorders and specifically claimed for the therapy of epilepsy. Other exemplified naphthalene derivatives include the following:

311371

N-[4-[2(*R*)-[1(*R*)-[3,5-Bis(trifluoromethyl)phenyl]ethoxy]-3(*S*)-(4-fluorophenyl)morpholin-4-ylmethyl]-1*H*-1,2,3-triazol-5-ylmethyl]-*N,N*-dimethylamine hydrochloride



C26 H28 F7 N5 O2 . HCl; Mol wt: 611.9871

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SOURCE – Merck & Co.

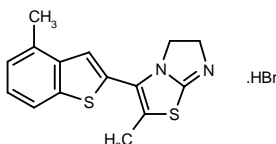
REFERENCES

1. Crocker, L. et al. (Merck & Co., Inc.) *Polymorphic form of a tachykinin receptor antagonist*. WO 0132656.

2. Harrison, T. et al. *An orally active, water-soluble neurokinin-1 receptor antagonist suitable for both intravenous and oral clinical administration*. J Med Chem 2001, 44(24): 4296.

310391

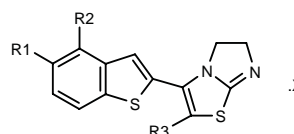
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Alzheimer's disease, cerebral ischemia, obsessive-compulsive disorders, panic, social phobias, bulimia, anorexia, type 2 diabetes, hyperglycemia and hyperlipidemia, stress and smoking cessation. Further applications include the treatment and prevention of metabolic diseases, sexual dysfunction, sleep apnea, premenstrual syndrome, urinary incontinence, etc., as well as the prevention of cardiovascular diseases, reduction of platelet adhesion and aiding in weight loss after pregnancy or smoking cessation. Other exemplified 1-benzothiazole-containing compounds include the following:



Compound	R1	R2	R3	X	Formula
310392	H	Cl	H	HBr	C ₁₃ H ₉ ClN ₂ S ₂ ·HBr
310393	H	Cl	CH ₂ OH		C ₁₄ H ₁₁ ClN ₂ OS ₂
310394	F	H	CH ₃	HBr	C ₁₄ H ₁₃ FN ₂ S ₂ ·HBr

SOURCE – Knoll (Abbott).

REFERENCES

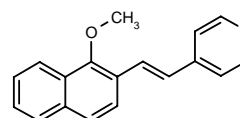
1. Doyle, K.J. et al. (Knoll AG) *Dihydroimidazol[2,1-*b*]thiazole and dihydro-5*H*-thiazolo[3,2-*a*]pyrimidines as antidepressant agents*. WO 0168653.

NEUROLOGIC DRUGS

ANTIEPILEPTIC DRUGS

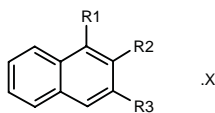
311325

4-[2-(1-Methoxynaphthalen-2-yl)vinyl]pyridine



C18 H15 N O; Mol wt: 261.3225

ACTION – Ionotropic glutamate receptor antagonist that acts at the low-affinity GluR6 kainate receptor. Potentially useful for the treatment of a variety of neurological disorders and specifically claimed for the therapy of epilepsy. Other exemplified naphthalene derivatives include the following:



Compound	R1	R2	R3	X	Formula
311326	OMe	4-Pyr-CH2CH2	H		C ₁₈ H ₁₇ NO
311327	Br	4-Pyr-CH=CH	H		C ₁₇ H ₁₂ BrN
311328	Cl	4-Pyr-CH2CH2	H		C ₁₇ H ₁₄ ClN
311329	CF3	4-Pyr-CH=CH	H		C ₁₈ H ₁₂ F ₃ N
311330	H	4-Pyr-CH=CH	Me		C ₁₈ H ₁₅ N
311331	OMe	4-pyrimidinyl-CH=CH	H		C ₁₇ H ₁₄ N ₂ O
311333	H	3-F-4-Pyr-CH=CH	H	HCl	C ₁₇ H ₁₂ FN.HCl
311334	OMe	4-Pyr-OCO	H		C ₁₇ H ₁₃ NO ₃

SOURCE – Lilly.

REFERENCES

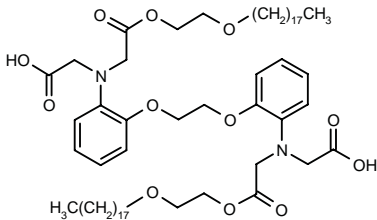
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TREATMENT OF EXTRAPYRAMIDAL MOVEMENT DISORDERS

DP-109

310666

2,2'-(Ethylenedioxy)bis(1,2-phenylene)bis[*N*-[2-[2-(octadecyloxy)ethoxy]-2-oxoethyl]imino]bis(acetic acid)



C62 H104 N2 O12; Mol wt: 1069.5060

ACTION – Lipophilic transition metal chelator with neuroprotective activity in a 6-OHDA-induced substantia nigra lesion model of Parkinson’s disease in rats. Compound at doses of 10-500 µg/kg/day p.o dose-dependently reduced both the rate of increase and the number of rotations induced by apomorphine in 6-OHDA-lesioned rats and also protected against neuronal loss observed 2 months after injury. Potentially useful for the treatment of neurodegenerative disorders such as Parkinson’s disease and Alzheimer’s disease.

SOURCE – D-Pharm.

REFERENCES

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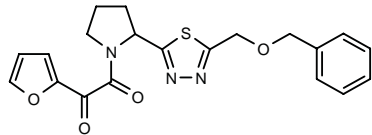
2. Friedman, J.E. et al. *DP-109, a lipophilic metal chelator, attenuates asymmetric rotations in the 6-hydroxydopamine partial lesion model of Parkinson's disease in the adult rat*. Soc Neurosci Abst 2001, 27: Abst 200.1.

3. Kalendarev, T. et al. *The unusual gradient elution for reversed phase HPLC of a strong chelator as an active drug substance*. J Pharm Biomed Anal 2001, 24(5-6): 967.

TREATMENT OS NEURODEGENERATIVE DISEASES

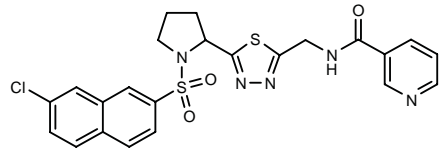
310966

1-[2-[5-(Benzyloxymethyl)-1,3,4-thiadiazol-2-yl]pyrrolidin-1-yl]-2-(2-furyl)ethane-1,2-dione



C20 H19 N3 O4 S; Mol wt: 397.4531

ACTION – Agent with the ability to potentiate neurite outgrowth, as demonstrated by enhancement of nerve growth factor (NGF)-induced outgrowth of neurites in PC-12 cells. Potentially useful in the treatment of peripheral nervous diseases such as neuropathy, diabetic neuropathy, neurectomy, amyotrophic lateral sclerosis, multiple sclerosis, as well as CNS disorders including Alzheimer’s disease, Parkinson’s disease, Huntington’s chorea and spinal cord injury. Another exemplifie compound within this series of pyrrolidine and piperidine derivatives is:



310967: C23 H20 Cl N5 O3 S2

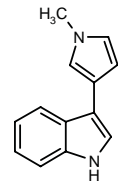
SOURCE – Japan Tobacco.

REFERENCES

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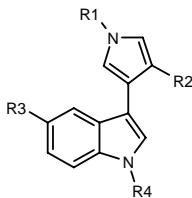
311466

3-(1-Methyl-1*H*-pyrrol-3-yl)-1*H*-indole



C13 H12 N2; Mol wt: 196.2518

ACTION – Cell death inhibitor proven to inhibit sodium nitroprusside-induced death of porcine ovarian granulosa cells and rat cerebellar granule cells with a minimum effective concentration (MEC) of 0.3 μ M and cell viability of > 95%. At 10 μ M, compound was also associated with > 95% cell viability in antimycin A-treated rat cerebellar granule cells. Potentially useful for the treatment of neurodegenerative diseases such as Alzheimer’s disease, spinal muscular atrophy, amyotrophic lateral sclerosis, Parkinson’s disease and Huntington’s chorea, as well as other conditions including glaucoma, muscular dystrophy, stroke, myocardial infarction, viral and autoimmune myocarditis, hepatitis, nephropathies, AIDS, toxic epidermal necrolysis, inflammatory dermatopathies, drug- and radiation-induced disorders, sepsis, insulin-dependent diabetes, Creutzfeldt-Jakob disease, and as a cell, tissue and organ preservation agent. Other exemplified pyrrole-substituted indoles are:



Compound	R1	R2	R3	R4	Formula
311467	Me	H	Me	H	C ₁₄ H ₁₄ N ₂
311468	H	CN	H	Me	C ₁₄ H ₁₁ N ₃
311469	Me	CN	H	Me	C ₁₅ H ₁₃ N ₃
311470	H	CO ₂ Et	H	Me	C ₁₆ H ₁₆ N ₂ O ₂
311471	Me	CO ₂ Et	H	Me	C ₁₇ H ₁₈ N ₂ O ₂
311472	Me	CO ₂ H	H	Me	C ₁₅ H ₁₄ N ₂ O ₂
311473	Me	CONHC14H29	H	Me	C ₂₉ H ₄₃ N ₃ O
311474	H	Me	H	Me	C ₁₄ H ₁₄ N ₂
311475	Me	Me	H	Me	C ₁₅ H ₁₆ N ₂
311476	Me	Ph	H	Me	C ₂₀ H ₁₈ N ₂

SOURCE – Sagami.

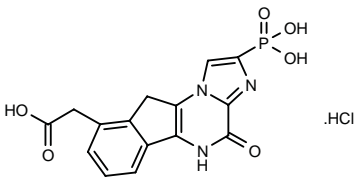
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RPR-119990

311241

2-(4-Oxo-2-phosphono-5,10-dihydro-4*H*-imidazo[1,2-*a*]-indeno[1,2-*e*]pyrazin-9-yl)acetic acid hydrochloride



C15 H12 N3 O6 P . HCl; Mol wt: 397.7097

ACTION– AMPA receptor antagonist with selective affinity for rat brain AMPA receptors (K_i = 107 nM) over a panel of other receptors, ion channels, binding sites and transporters, except for the kainate glutamate receptor (61% inhibition of binding at 10 μ M). Compound antagonized the response to kainic acid in *Xenopus* oocytes expressing human AMPA receptors (K_B = 71 nM), and it also blocked kainate-evoked currents in rat cerebellar granule neurons and electrically evoked field excitatory postsynaptic potentials (EPSPs) in rat hippocampal slices, with respective IC_{50} values of 50 and 93 nM. Compound antagonized hippocampal evoked responses *in vivo* after s.c. administration, demonstrating brain penetration at active concentrations. It exhibited potent and relatively long-lasting activity against electroshock-induced convulsions in mice (ED_{50} = 0.86 mg/kg i.v. and 2.3 mg/kg s.c.). In familial amyotrophic lateral sclerosis (ALS) *SOD1* transgenic mice, compound at a dose of 3 mg/kg/day s.c. significantly increased muscle strength and survival, as well as improving glutamate uptake in spinal cord. Pharmacokinetic studies in mice showed that compound given s.c. is rapidly absorbed and eliminated (t_{max} = 0.5-1 h and $t_{1/2}$ = 0.7-1.2 h), with a bioavailability of 54.5-70.5% and low brain penetration (< 4% of systemic exposure). The compound showed extremely low oral bioavailability (about 1%). Potentially useful for the treatment of ALS in combination with riluzole.

SOURCE – Aventis Pharma.

REFERENCES

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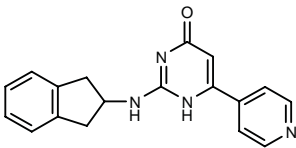
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4. Jimonet, P. et al. *Bioisosteres of 9-carboxymethyl-4-oxo-imidazo[1,2-*a*]indeno-[1,2-*e*]pyrazin-2-carboxylic acid derivatives. Progress towards selective, potent in vivo AMPA antagonists wit longer durations of action*. Bioorg Med Chem Lett 2001, 11(2): 127.

TREATMENT OF COGNITION DISORDERS

310241

2-(2,3-Dihydro-1*H*-inden-2-ylamino)-6-(4-pyridyl)pyrimidin-4(1*H*)-one



C18 H16 N4 O; Mol wt: 304.3514

ACTION – Glycogen synthase kinase 3β (GSK3β) inhibitor, potentially useful for the treatment of neuro-degenerative diseases, particularly Alzheimer’s disease, Parkinson’s disease, frontoparietal dementia, corticobasal degeneration, Pick’s disease, cerebrovascular accidents, brain and spinal cord trauma and peripheral neuropathies.

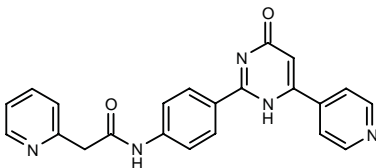
SOURCES – Mitsubishi Pharma; Sanofi-Synthélabo.

REFERENCES

1. Almario-Garcia, A. et al. (Sanofi-Synthélabo;Mitsubishi Pharma Corp.) 2-[Indanyl-amino]pyrimidone and 2-[tetrahydronaphthalenylamino]pyrimidone derivs. EP 1136486, WO 0170725.

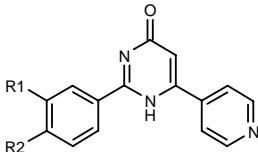
310242

N-[4-[4-Oxo-6-(4-pyridyl)-1,4-dihydropyrimidin-2-yl]-phenyl]-2-(2-pyridyl)acetamide



C22 H17 N5 O2; Mol wt: 383.4093

ACTION – Glycogen synthase kinase 3β (GSK3β) inhibitor, potentially useful for the treatment of neuro-degenerative diseases, particularly Alzheimer’s disease, Parkinson’s disease, frontoparietal dementia, corticobasal degeneration, Pick’s disease, cerebrovascular accidents, brain and spinal cord trauma and peripheral neuropathies. Other specifically claimed 2-phenylpyrimidin-4-one derivatives are:



Compound	R1	R2	Formula
310243	NHSO2CH2Ph	H	C22H18N4O3S
310244	H	NHCO(CH2)3CO2Me	C21H20N4O4
310245	H	NHCO(CH2)3CO2H	C20H18N4O4
310246	H	1-Pip-CO(CH2)3CONH	C25H27N5O3
310248	H	NHCOCH2Cl	C17H13ClN4O2
310249	H	4-Me-1-Piz-CH2CONH	C22H24N6O2
310250	H	CH2NHCOCH2CH2CO2Me	C21H20N4O4
310251	H	CH2NHCOCH2CH2CO2H	C20H18N4O4

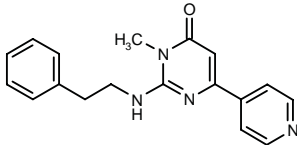
SOURCES – Mitsubishi Pharma; Sanofi-Synthélabo.

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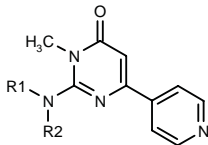
310252

3-Methyl-2-(2-phenylethylamino)-6-(4-pyridyl)pyrimidin-4(3H)-one



C18 H18 N4 O; Mol wt: 306.3672

ACTION – Glycogen synthase kinase 3β (GSK3β) inhibitor, potentially useful for the treatment of neuro-degenerative diseases, particularly Alzheimer’s disease, Parkinson’s disease, frontoparietal dementia, corticobasal degeneration, Pick’s disease, cerebrovascular accidents, brain and spinal cord trauma and peripheral neuropathies. Other specifically claimed pyrimidinone derivatives are:



Compound	R1	R2	Formula
310253	H	2-F-PhCH2CH2	C18H17FN4O
310254	H	4-NH2-PhCH2CH2	C18H19N5O
310255	H	4-(NH2SO2)-PhCH2CH2	C18H19N5O3S
310256	H	3-(NH2CH2)-PhCH2	C18H19N5O
310257	H	5-MeO-3-indolyl-CH2CH2	C21H21N5O2
310258	Me	1-Me-3-indolyl-CH2CH2	C22H23N5O
310259		-(CH2)4-	C14H16N4O

SOURCES – Mitsubishi Pharma; Sanofi-Synthélabo.

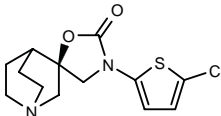
REFERENCES

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310291

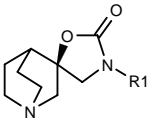
(3*R*)-3’-(5-Chlorothien-2-yl)spiro[1-azabicyclo[2.2.2]-octane-3,5’-oxazolidin]-2’-one

(3’*R*)-3-(5-Chlorothien-2-yl)spiro[oxazolidine-5,3’-quinuclidin]-2-one



C13 H15 Cl N2 O2 S; Mol wt: 298.7925

ACTION – Agent with potent and selective affinity for nicotinic acetylcholine $\alpha 7$ receptors, as demonstrated in binding assays by a K_i value of 9 nM against [125 I]- α -bungarotoxin binding in rat hippocampus membranes ($\alpha 7$ nicotinic receptors) compared to a K_i value of 1800 nM against [3 H]-cytisine binding in rat cerebral cortex membranes ($\alpha 4\beta 2$ nicotinic receptors). *In vivo*, it was found to ameliorate learning and memory impairment induced by methyllycaconitine (MLA) or MK-801 in mice (ED_{50} = 0.34 and 0.59 mg/kg p.o., respectively). Potentially useful in the treatment of Alzheimer’s disease, attention deficit disorder, anxiety, depression, schizophrenia, epilepsy, pain, Tourette’s syndrome, Parkinson’s disease and Huntington’s chorea, as well as in smoking cessation. Other exemplified compounds from this series of spiro compounds include the following:



Compound	R1	Formula
310292	5-Et-2-thienyl	C ₁₅ H ₂₀ N ₂ O ₂ S
310294	5-benzothieryl	C ₁₇ H ₁₈ N ₂ O ₂ S
310296	5-Br-2-thienyl	C ₁₃ H ₁₅ BrN ₂ O ₂ S

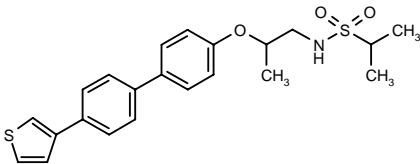
SOURCE – Mitsubishi Pharma.

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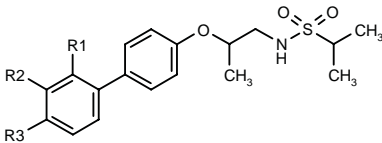
310433

N-[2-[4’-(3-Thienyl)biphenyl-4-yloxy]propyl]isopropane-sulfonamide



C22 H25 N O3 S2; Mol wt: 415.5755

ACTION – Glutamate receptor potentiator, potentially useful for the treatment of Alzheimer’s disease, depression, psychosis and cognitive deficits associated therewith. Other exemplified sulfonamide derivatives include the following:



Compound	R1	R2	R3	Isomer	Formula
310434	H	H	Cl		C ₁₈ H ₂₂ ClNO ₃ S
310435	H	H	CHO		C ₁₉ H ₂₃ NO ₄ S
310436	CHO	H	H		C ₁₉ H ₂₃ NO ₄ S
310437	H	H	CN		C ₁₉ H ₂₂ N ₂ O ₃ S
310438	H	i-PrSO2NH	H		C ₂₁ H ₃₀ N ₂ O ₅ S ₂
310439	H	H	CH2NHSO2Me		C ₂₀ H ₂₈ N ₂ O ₅ S ₂
310441	H	H	CH2CH2NHAc		C ₂₂ H ₃₀ N ₂ O ₄ S
310442	H	H	CN	S	C ₁₉ H ₂₂ N ₂ O ₃ S

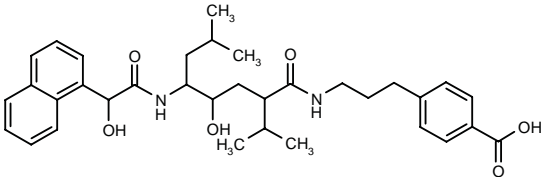
SOURCE – Lilly.

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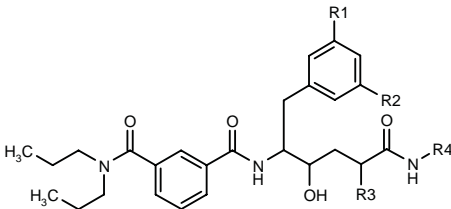
310689

4-[3-[4-Hydroxy-5-[2-hydroxy-2-(1-naphthyl)acetamido]-2-isopropyl-7-methyloctanamido]propyl]benzoic acid



C34 H44 N2 O6; Mol wt: 576.7296

ACTION – Peptidomimetic compound that acts as a β -secretase inhibitor and prevents the formation of β -amyloid peptide from β -amyloid precursor protein. Potentially useful for the treatment of Alzheimer’s disease, Down’s syndrome, hereditary cerebral hemorrhage with amyloidosis of the Dutch type, cerebral amyloid angiopathy, degenerative dementias and dementia associated with Parkinson’s disease. Other specifically claimed compounds are:



Compound	R1	R2	R3	R4	Formula
310690	H	H	Et	cis,cis-3,5-(CO2Me)2-cyclohexyl	C ₃₈ H ₅₃ N ₃ O ₈
310691	H	H	Et	(CH2)5CO2H	C ₃₄ H ₄₉ N ₃ O ₆
310692	F	F	Et	(CH2)7CO2Me	C ₃₇ H ₅₃ F ₂ N ₃ O ₆
310693	F	F	Et	trans-4-CO2H-cyclohexyl-CH2	C ₃₆ H ₄₉ F ₂ N ₃ O ₆
310694	F	F	CH2Ph	trans-4-CO2H-cyclohexyl-CH2	C ₄₁ H ₅₁ F ₂ N ₃ O ₆
310695	F	F	Me	trans-4-CO2H-cyclohexyl-CH2	C ₃₅ H ₄₇ F ₂ N ₃ O ₆
310696	F	F	Pr	trans-4-CO2H-cyclohexyl-CH2	C ₃₇ H ₅₁ F ₂ N ₃ O ₆

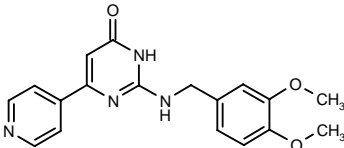
SOURCE – Elan.

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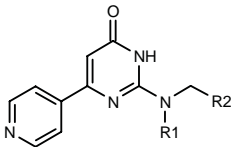
310858

2-(3,4-Dimethoxybenzylamino)-6-(4-pyridyl)pyrimidin-4(3*H*)-one



C18 H18 N4 O3; Mol wt: 338.3652

ACTION – Glycogen synthase kinase 3 (GSK3β) inhibitor, expected to be useful for the treatment of neurodegenerative diseases such as Alzheimer's disease. Other exemplified 2-(arylalkylamino)pyrimidine derivatives are:



Compound	R1	R2	Formula
310859	H	2,4-(Cl)2-PhCH2	C ₁₇ H ₁₄ Cl ₂ N ₄ O
310860	H	3-Cl-PhCH2	C ₁₇ H ₁₅ ClN ₄ O
310861	H	4-Cl-Ph	C ₁₆ H ₁₃ ClN ₄ O
310862	H	3-Cl-Ph	C ₁₆ H ₁₃ ClN ₄ O
310863	H	3-(MeSO2NHCH2)-Ph	C ₁₈ H ₁₉ N ₅ O ₃ S
310865	H	4-MeO-PhCH2CH2	C ₁₉ H ₂₀ N ₄ O ₂
310866	H	4-Ph-PhCH2CH2	C ₂₄ H ₂₂ N ₄ O
310867	CF3	CH2CH2Ph	C ₁₉ H ₁₇ F ₃ N ₄ O

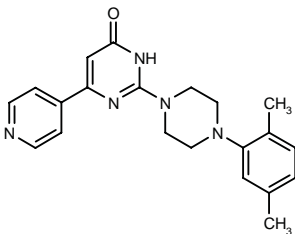
SOURCES – Mitsubishi Pharma; Sanofi-Synthélabo.

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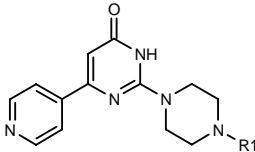
310872

2-[4-(2,5-Dimethylphenyl)piperazin-1-yl]-6-(4-pyridyl)pyrimidin-4(3*H*)-one



C21 H23 N5 O; Mol wt: 361.4467

ACTION – Glycogen synthase kinase 3 (GSK3β) inhibitor, expected to be useful for the treatment of neurodegenerative diseases such as Alzheimer's disease. Other exemplified 2-(nitrogen-containing heterocyclic)pyrimidine derivatives are:



Compound	R1	Formula
310873	4-Cl-Ph	C ₁₉ H ₁₈ ClN ₅ O
310874	2-pyrimidinyl	C ₁₇ H ₁₇ N ₇ O
310876	3-CF3-2-Pyr	C ₁₉ H ₁₇ F ₃ N ₆ O
310878	5-MeO-3-indolyl	C ₂₂ H ₂₂ N ₆ O ₂
310879	6,7-(MeO)2-1,2,3,4-tetrahydro-2-Naph	C ₂₅ H ₂₉ N ₅ O ₃
310881	thieno[3,2-c]pyridin-4-yl	C ₂₀ H ₁₈ N ₆ OS
310884	1-Me-3-indolyl	C ₂₂ H ₂₂ N ₆ O

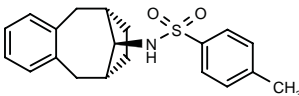
SOURCES – Mitsubishi Pharma; Sanofi-Synthélabo.

REFERENCES

1. Almario-Garcia, A. et al. (Sanofi-Synthélabo;Mitsubishi Pharma Corp.) *2-(Nitrogen-heterocyclic)pyrimidone derivs*. EP 1136483, EP 1136489, EP 1136493, WO 0170728.

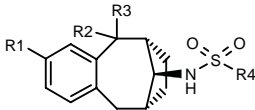
311013

syn-4-Methyl-*N*-(tricyclo[8.2.1.0^{3,8}]-3,5,7-tridecatrien-13-yl)benzenesulfonamide

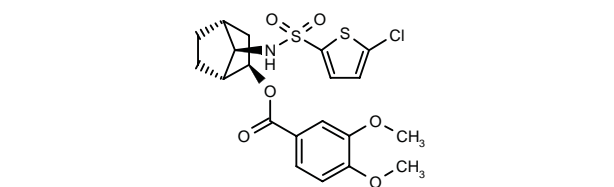


C20 H23 N O2 S; Mol wt: 341.4727

ACTION – Agent with γ-secretase-inhibitory activity and potential in the prevention and treatment of Alzheimer's disease. Other exemplified sulfonamido-substituted bridged bicyclic compounds include the following:



Compound	R1	R2	R3	R4	Formula
311014	H	H	H	2-Pyr	C ₁₈ H ₂₀ N ₂ O ₂ S
311015	NHCO2CH2Ph	H	H	Ph	C ₂₇ H ₂₈ N ₂ O ₄ S
311016	4-F-PhCH2NH	H	H	Ph	C ₂₆ H ₂₇ FN ₂ O ₂ S
311018	4-Pyr-CH2O	H	H	Ph	C ₂₅ H ₂₆ N ₂ O ₃ S
311019	H	H	H	CH2CH2OEt	C ₁₇ H ₂₆ NO ₃ S
311020	4-F-PhOCH2CH2O	H	H	2-thienyl	C ₂₅ H ₂₆ FNO ₄ S ₂
311021	4-morpholinyl-CH2CH2O	H	H	3-Pyr	C ₂₄ H ₃₁ N ₃ O ₄ S
311023	4-F-PhOCH2CH2O	-CH2-		3-Pyr	C ₂₇ H ₂₇ FN ₂ O ₄ S



311017: C20 H22 Cl N O6 S2

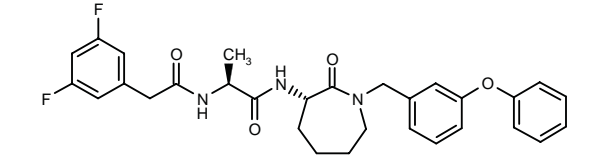
SOURCES – Merck Frosst; Merck Sharp & Dohme.

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311060

*N*²-[2-(3,5-Difluorophenyl)acetyl]-*N*¹-[2-oxo-1-(3-phenoxybenzyl)perhydroazepin-3(S)-yl]-L-alaninamide



C30 H31 F2 N3 O4; Mol wt: 535.5879

ACTION – A representative compound from a series of lactams with the ability to inhibit the production of β -amyloid (A β) peptide, reported to act through inhibition of γ -secretase. Potentially useful for the treatment of diseases related to A β production such as Alzheimer's disease and Down's syndrome.

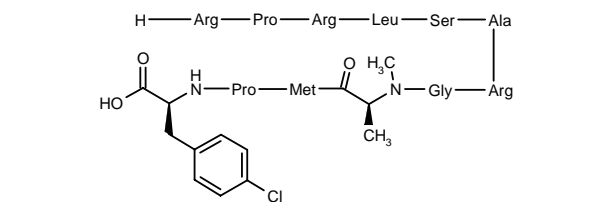
SOURCE – Bristol-Myers Squibb.

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311165

L-Arginyl-L-prolyl-L-arginyl-L-leucyl-L-seryl-L-alanyl-L-arginyl-glycyl-*N*-methyl-L-alanyl-L-methionyl-L-prolyl-4-chloro-L-phenylalanine



C60 H100 Cl N21 O14 S; Mol wt: 1407.1020

ACTION – A peptide G-protein-coupled receptor ligand shown to inhibit forskolin-induced cAMP production in CHO-A10 cells with an EC₅₀ of 0.27 nM. Potentially useful for the treatment of dementia of different origins, as well as a wide variety of other disorders including intoxication caused by alcohol, drugs and metal and organic compounds, depression, anxiety, schizophrenia, phobia, growth hormone secretion disorders, polyphagia, hyperlipidemia, diabetes, cancer, pancreatitis, nephropathy, arthritis, spinal cord injury, amyotrophic lateral sclerosis, acute myocardial infarction, osteoporosis, asthma, epilepsy, etc. Other peptide derivatives are:

H-Arg-Arg- Gln-Arg-Pro-Arg-Leu-Ser-A-Gly-Pro-R1

Compound	R1	A	Formula
311166	-L-Nle-L-Pro-L-Tyr-OH	-L-His-L-Lys-	C ₈₂ H ₁₃₇ N ₃₁ O ₁₉
311167	-L-Met-OH	-L-Ala-L-Arg-	C ₆₄ H ₁₁₇ N ₂₉ O ₁₆ S
311168	-L-Met-L-Pro-(4-Cl)-L-Phe-OH	-L-Ala-L-Arg-	C ₇₈ H ₁₃₂ ClN ₃₁ O ₁₈ S

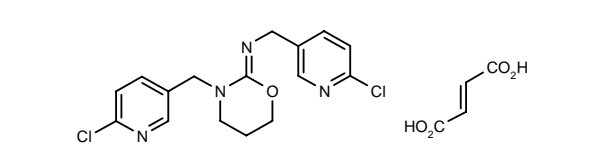
SOURCE – Takeda.

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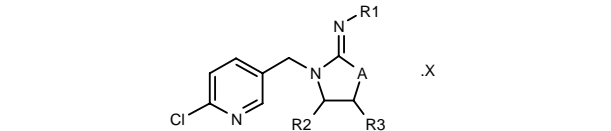
311488

3,*N*-Bis(6-chloropyridin-3-ylmethyl)perhydro-1,3-oxazin-2-imine fumarate



C16 H16 Cl2 N4 O . C4 H4 O4; Mol wt: 467.3070

ACTION – Nicotinic acetylcholine $\alpha 4\beta 2$ receptor agonist with a K_i value of 22 nM against this receptor in rat brain preparations. Potentially useful for the treatment of dementia associated with various disorders (senile and presenile dementia, Alzheimer's disease, dementia associated with Down's syndrome and AIDS, cerebrovascular dementia), as well as for the treatment of Parkinson's disease, Tourette's syndrome, nervous symptoms associated with the chronic period of cerebral infarction, head injury, anxiety, schizophrenia, depression, Huntington's chorea and pain. *In vitro*, compound was able to activate human $\alpha 4\beta 2$ receptors expressed in *Xenopus* oocytes. Other exemplified heterocyclic imino compounds include the following:



Compound	R1	R2	R3	A	X	Formula
311490	6-Cl-3-Pyr-CH2	H	H	S	fumarate	C ₁₅ H ₁₄ Cl ₂ N ₄ S.C ₄ H ₄ O ₄
311492	6-Cl-3-Pyr-CH2	bond	S	S	oxalate	C ₁₅ H ₁₂ Cl ₂ N ₄ S.C ₂ H ₂ O ₄
311493	H	bond	N(Me)	fumarate		C ₁₀ H ₁₁ ClN ₄ .C ₄ H ₄ O ₄

SOURCE – Suntory.

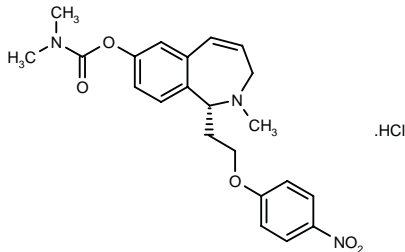
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RS-1439

311251

N,N-Dimethylcarbamic acid 2-methyl-1(*R*)-[2-(4-nitro-phenoxy)ethyl]-2,3-dihydro-1*H*-2-benzazepin-7-yl ester hydrochloride



C22 H25 N3 O5 . HCl; Mol wt: 447.9164

ACTION – Dual acetylcholinesterase (AChE) and selective serotonin reuptake inhibitor (SSRI), a derivative of RS-1233. It strongly inhibited both AChE (IC₅₀ = 14 nM) and 5-HT reuptake (IC₅₀ = 6 nM) and represents a potential treatment for Alzheimer’s disease and associated depression.

SOURCE – Sankyo.

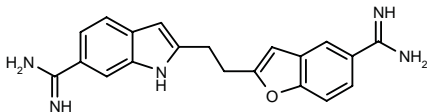
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TREATMENT OF CEREBROVASCULAR DISEASES

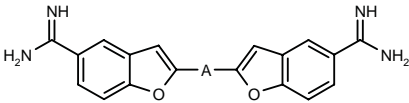
311202

2-[2-(5-Amidino-1-benzofuran-2-yl)ethyl]-1*H*-indole-6-carboxamide



C20 H19 N5 O; Mol wt: 345.4041

ACTION – An inhibitor of the Na⁺/H⁺ exchanger subtype 3 (NHE-3) with an IC₅₀ of 0.98 μM versus 4.6 and 47.6 μM for inhibition of NHE-1 and NHE-2, respectively. Potentially useful for the treatment of thrombosis, ischemic disorders, stroke, shock states, proliferative disorders and renal disorders. Other exemplified bisamidino compounds are:



Compound	A	Formula
311203	-(CH2)4-	C ₂₂ H ₂₂ N ₄ O ₂
311204	-(CH2)6-	C ₂₄ H ₂₆ N ₄ O ₂

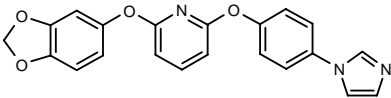
SOURCE – Merck KGaA.

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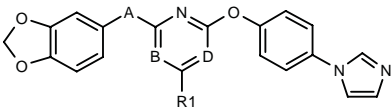
311225

2-(1,3-Benzodioxol-5-yloxy)-6-[4-(1*H*-imidazol-1-yl)-phenoxy]pyridine



C21 H15 N3 O4; Mol wt: 373.3665

ACTION – An inhibitor of inducible nitric oxide synthase (iNOS), potentially useful for the treatment of multiple sclerosis, stroke, Alzheimer’s disease, HIV dementia, Parkinson’s disease, meningitis, congestive heart failure, atherosclerosis, restenosis, septic shock, asthma, adult respiratory distress syndrome, arthritis, glomerulo-nephritis, systemic lupus erythematosus and inflammatory bowel disease, among other NO-mediated conditions. Other specifically claimed compounds include the following:



Compound	R1	A	B	D	Formula
311226	Me	O	C(F)	C(F)	C ₂₂ H ₁₅ F ₂ N ₃ O ₄
311229	Me	-CH2NH-	C(F)	C(F)	C ₂₃ H ₁₈ F ₂ N ₄ O ₃
311231	H	O	CH	N	C ₂₀ H ₁₄ N ₄ O ₄
311232	H	O	N	CH	C ₂₀ H ₁₄ N ₄ O ₄
311233	H	O	N	N	C ₂₀ H ₁₄ N ₄ O ₄

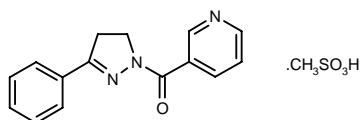
SOURCE – Schering AG.

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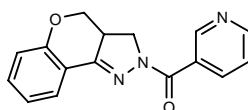
311517

1-(3-Phenyl-4,5-dihydro-1*H*-pyrazol-1-yl)-1-(3-pyridyl)-methanone methanesulfonate



C15 H13 N3 O . C H4 O3 S; Mol wt: 347.3933

ACTION – An activator of the glutamic acid transporter shown to increase glutamic acid uptake *in vitro* and reduce infarct area in a middle cerebral artery occlusion model in rats. No deaths were observed in mice 24 h following a dose of 100 mg/kg i.p. Potentially useful for the treatment of cerebral ischemic disorders and amyotrophic lateral sclerosis, among others. Another exemplified compound from this series of pyrazoline and tetrahydropyridazine derivatives is:



311518: C16 H13 N3 O2

SOURCE – Mitsui Chemicals.

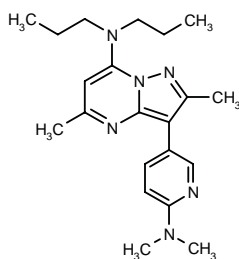
REFERENCES

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R-121920*

255944

N-[3-[6-(Dimethylamino)pyridin-3-yl]-2,5-dimethylpyrazolo[1,5-*a*]pyrimidin-7-yl]-*N,N*-dipropylamine



C21 H30 N6; Mol wt: 366.5130

ACTION – Corticotropin-releasing factor CRF₁ antagonist with high selectivity over CRF₂ receptors ($K_i = 4$ nM and > 10 μ M, respectively), able to rapidly cross the blood–brain barrier in rats after i.v. administration, giving peak brain concentrations at 5 min approximately 2-fold higher than those in plasma. Compound exhibited neuroprotective activity in two rat models of permanent focal cerebral ischemia; in a subtemporal middle cerebral artery occlusion (MCAO) model, a dose of 10 mg/kg i.v. followed by 5 mg/kg s.c. every hour for 4 h significantly reduced total (40%) and cortical (37%) infarct volume, and in an intraluminal suture MCAO model, a dose of 10 mg/kg i.v. significantly reduced hemispheric infarct volume (34%) and brain swelling (50%). Potentially useful for the treatment of stroke.

SOURCES – Janssen; Neurocrine Biosciences.

REFERENCES

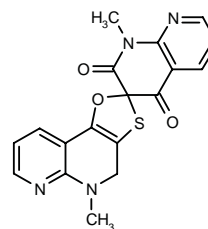
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2. Huang, C. et al. *A novel class of 3-(2-pyridyl)pyrazolo[3,2-*A*]pyrimidines as potent CRF1 receptor antagonists*. Soc Neurosci Abstr 2000, 26(Part 2): Abstr 807.2.
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*Identified compound **255944** (see **255011**) Drug Data Rep 1997, 019(11): 0967.

YM-215438

311252

1,5'-Dimethyl-2,2',3,4,4',5'-hexahydro-1*H*-spiro[1,8-naphthyridine-3,2'-[1,3]oxathio[4,5-*c*][1,8]naphthyridine]-2,4-dione



C18 H14 N4 O3 S; Mol wt: 366.3996

ACTION – Potent and selective, nonpeptide Zn²⁺-potentiated caspase 3 inhibitor, potentially useful for the treatment or prevention of disorders such as ischemic stroke, Parkinson's disease, Alzheimer's disease, myocardial infarction and liver failure.

SOURCE – Yamanouchi.

REFERENCES

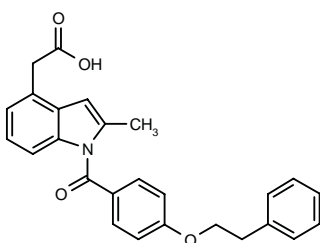
1. Ohmori, J. et al. *Discovery, synthesis, and SAR of novel non-peptide, small molecule and zinc(II) - Potentiated caspase-3 inhibitors*. 21st Symp Med Chem (Nov 28-30, Kyoto) 2001, Abstr 1P-30.

RESPIRATORY DRUGS

ASTHMA THERAPY

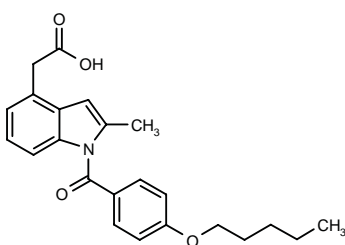
310271

2-[2-Methyl-1-[4-(2-phenylethoxy)benzoyl]-1*H*-indol-4-yl]acetic acid



C26 H23 N O4; Mol wt: 413.4707

ACTION – Prostaglandin DP receptor antagonist that gave a K_i of 0.0018 μ M against DP receptors in membranes of CHO cells, and inhibited PGD₂-induced production of cAMP with an IC₅₀ of 0.12 μ M. Potentially useful for the treatment of allergic diseases including allergic rhinitis, allergic conjunctivitis, atopic dermatitis, bronchial asthma, food allergy, systemic mastocytosis, anaphylactic shock, tracheal constriction, urticaria and eczema, as well as diseases accompanied by itching, inflammation, chronic obstructive pulmonary disease (COPD), reflow disturbance following ischemic conditions, cerebrovascular disease, pleuritis complicated by rheumatoid arthritis and ulcerative colitis. Another exemplified indole derivative is:



310272: C23 H25 N O4

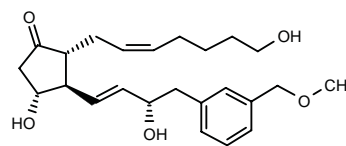
SOURCE – Ono.

REFERENCES

1. Torisu, K. et al. (Ono Pharmaceutical Co., Ltd.) *Indole derivs., process for preparation of the same and use thereof*. WO 0166520.

310285

1-Deoxo-16-[3-(methoxymethyl)phenyl]-17,18,19,20-tetranorprostaglandin E₂



C24 H34 O5; Mol wt: 402.5276

ACTION – Agent with high affinity for prostaglandin PGE₂ receptors, particularly the EP₄ subtype, potentially useful for the treatment or prevention of immune disorders, asthma, neurodegeneration, hepatic injury, acute hepatitis, nephritis, renal failure, hyper-tension, myocardial ischemia, sepsis and ulcerative colitis, among others. *In vivo*, compound was shown to inhibit lipopolysaccharide-stimulated TNF- α production in rats with an ID₅₀ value of 159 μ g/kg p.o. A representative compound from a series of ω -substituted phenyl-prostaglandin E alcohols.

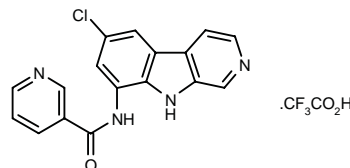
SOURCE – Ono.

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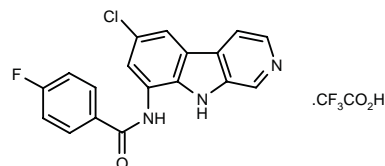
310461

N-(6-Chloro-9*H*-pyrido[3,4-*b*]indol-8-yl)pyridine-3-carboxamide trifluoroacetate



C17 H11 Cl N4 O . C2 H F3 O2; Mol wt: 436.7758

ACTION – Selective inhibitor of I κ B kinase (IKK; IC₅₀ = 0.052 μ M), potentially useful for the treatment of asthma, osteoarthritis, rheumatoid arthritis, Alzheimer's disease, carcinomatous disorders and cardiac infarct. In a mouse heterotopic cardiac transplant model, oral administration of this compound at 25 mg/kg/day for 14 days produced a delay in graft rejection from 7 days in controls to 20 days. Another exemplified compound from this series of substituted β -carbolines is:



310463: C18 H11 Cl F N3 O . C2 H F3 O2

SOURCE – Aventis Pharma.

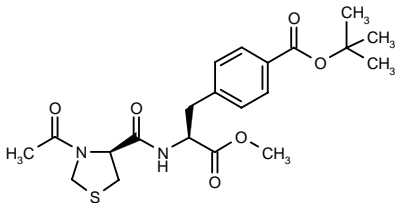
REFERENCES

1. Ritzeler, O. et al. (Aventis Pharma Deutschland GmbH) *Substd. beta-carbolines as IkB-kinase inhibiting activity*. EP 1134221, WO 0168648.

310518

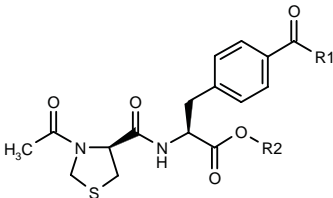
N-[3-Acetylthiazolidin-4 (S)-ylcarbonyl]-4-(tert-butoxy-carbonyl)-L-phenylalanine methyl ester

N-Acetyl-4-thia-D-prolyl-4-(tert-butoxycarbonyl)-L-phenyl-alanine methyl ester

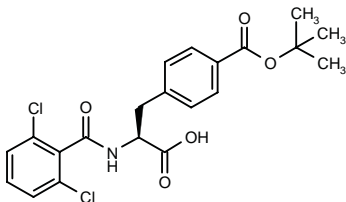


C21 H28 N2 O6 S; Mol wt: 436.5262

ACTION – An inhibitor of very late antigen-4 (VLA-4)-associated cell adhesion that acts through an interaction with $\alpha_4\beta_1$ and $\alpha_4\beta_7$ integrins. The compound is expected to be useful for the treatment of inflammatory, immune and autoimmune diseases, particularly asthma, arthritis, psoriasis, transplant rejection, multiple sclerosis, type 1 diabetes, inflammatory bowel disease, stem cell mobilization and engraftment, and sickle cell anemia. Other exemplified L-phenylalanine derivatives are:



Compound	R1	R2	Formula
310519	t-BuO	H	C ₂₀ H ₂₆ N ₂ O ₆ S
310520	OH	Me	C ₁₇ H ₂₀ N ₂ O ₆ S
310521	t-BuNH	Me	C ₂₁ H ₂₉ N ₃ O ₅ S
310522	2-Cl-6-Me-PhNH	Me	C ₂₄ H ₂₆ ClN ₃ O ₅ S
310523	2,6-(Cl)2-PhO	Me	C ₂₃ H ₂₂ Cl ₂ N ₂ O ₆ S



310524: C21 H21 Cl2 N O5

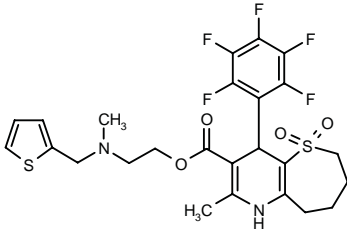
SOURCE – Novartis.

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1. Cooke, N.G. and Sabio, M.L. (Novartis-Erfindungen VmbH;Novartis AG) $\alpha_4\beta_1$ and $\alpha_4\beta_7$ integrin inhibitors. WO 0168586.

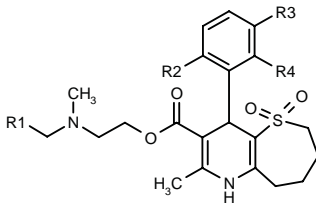
310636

2-Methyl-5,5-dioxo-4-(pentafluorophenyl)-1,4,6,7,8,9-hexahydrothiepino[3,2-*b*]pyridine-3-carboxylic acid 2-[N-methyl-N-(thien-2-ylmethyl)amino]ethyl ester



C25 H25 F5 N2 O4 S2; Mol wt: 576.6045

ACTION – Calcium channel antagonist, potentially useful in the treatment of asthma, as well as hypersensitivity, allergy, bronchospasm, dysmenorrhea, esophageal spasms, glaucoma, preterm labor, urinary tract disorders, gastrointestinal motility disorders and cardiovascular disorders including hypertension, ischemia, angina pectoris, congestive heart failure, myocardial infarction and stroke. Other exemplified thiepino[3,2-*b*]pyridines include the following:



Compound	R1	R2	R3	R4	Formula
310640	2-thienyl	F	H	Cl	C ₂₅ H ₂₆ ClF ₅ N ₂ O ₄ S ₂
310641	2-thienyl	H	NO ₂	H	C ₂₅ H ₂₉ N ₃ O ₆ S ₂
310643	2-thienyl	H	H	Cl	C ₂₅ H ₂₉ ClN ₂ O ₄ S ₂
310644	3-thienyl	H	NO ₂	H	C ₂₅ H ₂₉ N ₃ O ₆ S ₂

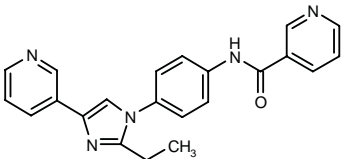
SOURCE – Ortho-McNeil.

REFERENCES

1. Henry, J.R. (Ortho-McNeil Pharmaceutical, Inc.) *Thiepino[3,2-b]dihydropyridines and related compsns. and methods*. WO 0170748.

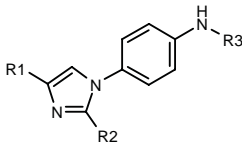
310765

N-[4-[2-Ethyl-4-(3-pyridyl)-1*H*-imidazol-1-yl]phenyl]pyridine-3-carboxamide

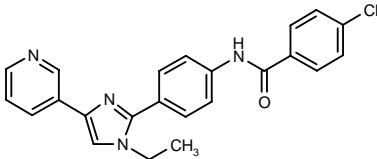


C22 H19 N5 O; Mol wt: 369.4261

ACTION – Antiinflammatory agent with the ability to inhibit IL-2 production and considered to have potential in the treatment of inflammatory and autoimmune diseases, particularly acute and chronic inflammation, allergies, contact dermatitis, psoriasis, rheumatoid arthritis, multiple sclerosis, type 1 diabetes, inflammatory bowel disease, Guillain-Barré syndrome, Crohn’s disease, ulcerative colitis, transplant rejection and lupus erythematosus. Other specifically claimed 4-aminophenyl-substituted imidazoles include the following:



Compound	R1	R2	R3	Formula
310766	3-Pyr	CN	6-[NC(CH2)3O]-3-Pyr-CH2	C ₂₅ H ₂₁ N ₇ O
310767	3-Pyr	Et	1-Me-2-indolyl-CO	C ₂₆ H ₂₃ N ₅ O
310768	3-Pyr	CN	2-Cl-6-Me-PhCH2	C ₂₃ H ₁₈ ClN ₅
310769	3-Pyr	Et	2-F-6-Me-PhCH2	C ₂₄ H ₂₃ FN ₄
310770	3-Pyr	CN	4-[1,3-dioxolan-(CH2)3O]-PhCO	C ₂₈ H ₂₈ N ₅ O ₄
310771	3-Pyr	CN	4-[NC(CH2)3O]-PhCH2	C ₂₆ H ₂₂ N ₆ O
310772	CF3	Me	4-Cl-PhCO	C ₁₈ H ₁₃ ClF ₃ N ₃ O



310773: C23 H19 Cl N4 O

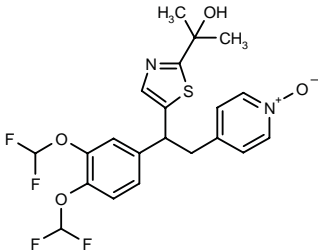
SOURCE – Boehringer Ingelheim.

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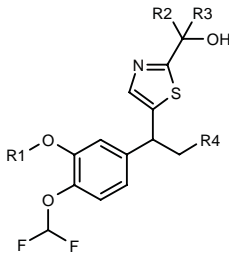
310915

2-[5-[1-[3,4-Bis(difluoromethoxy)phenyl]-2-(1-oxido-pyridin-4-yl)ethyl]thiazol-2-yl]propan-2-ol



C21 H20 F4 N2 O4 S; Mol wt: 472.4570

ACTION – Phosphodiesterase type 4 (PDE4) inhibitor, potentially useful in the treatment of asthma, chronic bronchitis, chronic obstructive pulmonary disease, eosinophilic granuloma, psoriasis, endotoxic shock, ulcerative colitis, Crohn’s disease, myocardial and brain reperfusion injury, arthritis, atopic dermatitis, adult and infant respiratory distress syndrome, and allergic rhinitis, among a wide variety of PDE4-mediated conditions. Other tri-aryl-substituted ethanes include the following:



Compound	R1	R2	R3	R4	Formula
310916	CHF2	CF3	CF3	4-Pyr	C ₂₁ H ₁₄ F ₁₀ N ₂ O ₃ S
310917	CHF2	Ph	H	1-oxido-4-Pyr	C ₂₅ H ₁₄ F ₄ N ₂ O ₄ S
310918	CHF2	Ph	Et	1-oxido-4-Pyr	C ₂₇ H ₂₄ F ₄ N ₂ O ₄ S
310919	CHF2	4-Et-Ph	Me	1-oxido-4-Pyr	C ₂₈ H ₂₆ F ₄ N ₂ O ₄ S
310920	CHF2	4-F-Ph	Me	1-oxido-4-Pyr	C ₂₆ H ₂₁ F ₅ N ₂ O ₄ S
310921	CHF2	-(CH2)3-		1-oxido-4-Pyr	C ₂₂ H ₂₀ F ₄ N ₂ O ₄ S
310922	cyclobutyl	CF3	CF3	4-Pyr	C ₂₄ H ₂₀ F ₈ N ₂ O ₃ S
310923	cyclobutyl	Me	Me	1-oxido-3-Pyr	C ₂₄ H ₂₆ F ₂ N ₂ O ₄ S
310924	cyclopropyl	Me	Me	1-oxido-4-Pyr	C ₂₃ H ₂₄ F ₂ N ₂ O ₄ S

SOURCE – Merck Frosst.

REFERENCES

1. Friesen, R. et al. (Merck Frosst Canada Inc.) *Tri-aryl-subst.-ethane PDE4 inhibitors.* WO 0170738.

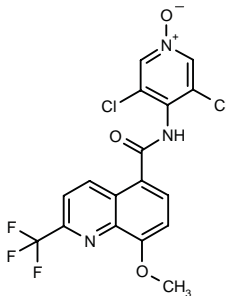
SCH-351591*

289736

3,5-Dichloro-4-[8-methoxy-2-(trifluoromethyl)quinolin-5-ylcarboxamido]pyridine-1-oxide

N-(3,5-Dichloro-1-oxidopyridin-4-yl)-8-methoxy-2-(trifluoromethyl)quinoline-5-carboxamide

D-4396



C17 H10 Cl2 F3 N3 O3; Mol wt: 432.1840

ACTION – Phosphodiesterase type 4 (PDE4) inhibitor with *in vivo* efficacy in animal models of respiratory diseases and a superior therapeutic index compared to previously reported PDE4 inhibitors. Compound is undergoing phase I clinical trials for the potential treatment of respiratory diseases such as asthma and chronic obstructive pulmonary disease (COPD).

SOURCES – Celltech Group; Schering-Plough.

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1. Dyke, H.J. and Montana, J.G. (Darwin Discovery Ltd.) *N-Oxides of heterocyclic cpds. with TNF and PDE-IV inhibiting activity*. EP 1045845, US 6262070, WO 0026208.

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3. Hunt, H.J. et al. *The profile of Sch351591, a novel phosphodiesterase 4 inhibitor*. Inflamm Res 2001, 50(Suppl. 3): Abst IS/17.

4. *Celltech Chiroscience and Medeva finalize merger*. DailyDrugNews.com (Daily Essentials) 2000, Jan 28.

5. *Chiroscience identifies development candidate from PDE4 collaboration with Schering-Plough*. DailyDrugNews.com (Daily Essentials) 1999, May 3.

6. *Major U.K. biopharmaceutical company merger announced*. DailyDrugNews.com (Daily Essentials) 1999, Nov 12.

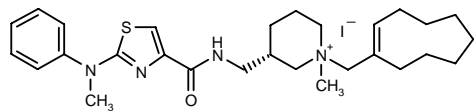
7. *New product pipeline*. Celltech Group plc Press Release 2000, March 22

*Identified compound **289736** Drug Data Rep 2000, 022(09): 0783.

TREATMENT OF CHRONIC
OBSTRUCTIVE PULMONARY
DISEASES

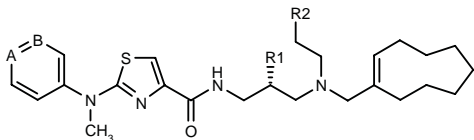
311527

1-(Cyclononen-1-ylmethyl)-1-methyl-3(S)-[2-(*N*-methyl-*N*-phenylamino)thiazol-4-ylcarboxamidomethyl]piperidinium iodide



C28 H41 I N4 O S; Mol wt: 608.6249

ACTION – Muscarinic M₃ receptor antagonist with a K_i of 1.4 nM against M₃ receptors expressed in CHO cells, exhibiting 110-, 180-, 34- and 930-fold selectivity over M₁, M₂, M₄ and M₅ receptor subtypes, respectively. Potentially useful for the treatment of respiratory diseases including chronic obstructive pulmonary disease, chronic bronchitis, asthma, pulmonary fibrosis, pulmonary emphysema and rhinitis, as well as urinary tract diseases such as pollakiuria, neurogenic bladder, nocturnal enuresis, unstable bladder and urinary incontinence, and digestive tract diseases including irritable bowel syndrome, spastic colitis, gastroduodenal ulcer and diverticulitis. Other exemplified thiazole-4-carboxamides are:



Compound	R1	R2	A	B	Formula
311528	-CH2-		CH	N	C ₂₆ H ₃₇ N ₅ OS
311529	-CH2-		N	CH	C ₂₆ H ₃₇ N ₅ OS
311531	H	OH	CH	CH	C ₂₆ H ₃₈ N ₄ O ₂ S

SOURCE – Banyu.

REFERENCES

1. Ohtake, K. et al. (Banyu Pharmaceutical Co., Ltd.) *Novel aminothiazole derivs*. JP 2001278872.

CARDIOVASCULAR DRUGS

ANTIHYPERTENSIVE DRUGS

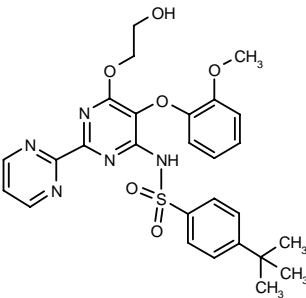
BOSENTAN⁺

Prop INN

203927

4-*tert*-Butyl-*N*-[6-(2-hydroxyethoxy)-5-(2-methoxyphen-
oxy)-2-(2-pyrimidinyl)pyrimidin-4-yl]benzenesulfonamide

Ro-47-0203



C27 H29 N5 O6 S; Mol wt: 551.6260

ACTION – Endothelin receptor antagonist.

INDICATION – To improve exercise ability and decrease the rate of clinical worsening in patients with pulmonary arterial hypertension with significant limitation of physical activity (WHO class III and IV).

PRESENTATION – Tablets, 62.5 and 125 mg.

PROPRIETARY NAME – Tracleer (CA, US).

SOURCE – Actelion.

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2. Hunt, H.J. et al. *The profile of SCH351591, a novel phosphodiesterase 4 inhibitor*. 11th RSC-SCI Med Chem Symp (Sept 9-12, Cambridge) 2001, Abst.

3. Hunt, H.J. et al. *The profile of Sch351591, a novel phosphodiesterase 4 inhibitor*. Inflamm Res 2001, 50(Suppl. 3): Abst IS/17.

4. *Celltech Chiroscience and Medeva finalize merger*. DailyDrugNews.com (Daily Essentials) 2000, Jan 28.

5. *Chiroscience identifies development candidate from PDE4 collaboration with Schering-Plough*. DailyDrugNews.com (Daily Essentials) 1999, May 3.

6. *Major U.K. biopharmaceutical company merger announced*. DailyDrugNews.com (Daily Essentials) 1999, Nov 12.

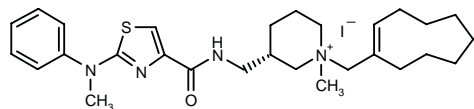
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*Identified compound **289736** Drug Data Rep 2000, 022(09): 0783.

TREATMENT OF CHRONIC
OBSTRUCTIVE PULMONARY
DISEASES

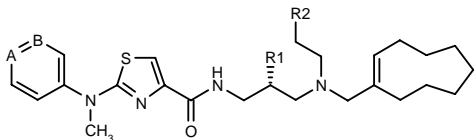
311527

1-(Cyclononen-1-ylmethyl)-1-methyl-3(S)-[2-(*N*-methyl-*N*-phenylamino)thiazol-4-ylcarboxamidomethyl]piperidinium iodide



C28 H41 I N4 O S; Mol wt: 608.6249

ACTION – Muscarinic M₃ receptor antagonist with a K_i of 1.4 nM against M₃ receptors expressed in CHO cells, exhibiting 110-, 180-, 34- and 930-fold selectivity over M₁, M₂, M₄ and M₅ receptor subtypes, respectively. Potentially useful for the treatment of respiratory diseases including chronic obstructive pulmonary disease, chronic bronchitis, asthma, pulmonary fibrosis, pulmonary emphysema and rhinitis, as well as urinary tract diseases such as pollakiuria, neurogenic bladder, nocturnal enuresis, unstable bladder and urinary incontinence, and digestive tract diseases including irritable bowel syndrome, spastic colitis, gastroduodenal ulcer and diverticulitis. Other exemplified thiazole-4-carboxamides are:



Compound	R1	R2	A	B	Formula
311528	-CH2-		CH	N	C ₂₆ H ₃₇ N ₅ OS
311529	-CH2-		N	CH	C ₂₆ H ₃₇ N ₅ OS
311531	H	OH	CH	CH	C ₂₆ H ₃₈ N ₄ O ₂ S

SOURCE – Banyu.

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CARDIOVASCULAR DRUGS

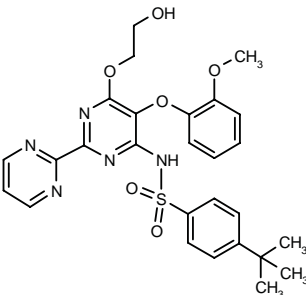
ANTIHYPERTENSIVE DRUGS

BOSENTAN⁺
Prop INN

203927

4-*tert*-Butyl-*N*-[6-(2-hydroxyethoxy)-5-(2-methoxyphen-
oxy)-2-(2-pyrimidinyl)pyrimidin-4-yl]benzenesulfonamide

Ro-47-0203



C27 H29 N5 O6 S; Mol wt: 551.6260

ACTION – Endothelin receptor antagonist.

INDICATION – To improve exercise ability and decrease the rate of clinical worsening in patients with pulmonary arterial hypertension with significant limitation of physical activity (WHO class III and IV).

PRESENTATION – Tablets, 62.5 and 125 mg.

PROPRIETARY NAME – Tracleer (CA, US).

SOURCE – Actelion.

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12. Rubin, L.J. et al. *BREATHE-1: Results of a multicenter, randomized, double-blind, placebo-controlled study of bosentan in pulmonary arterial hypertension (PAH)*. Arthritis Rheum 2001, 44(9, Suppl.): S266.

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22. *Actelion announces results from phase III trial in pulmonary hypertension*. DailyDrugNews.com (Daily Essentials) 2000, May 12.

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26. *FDA advisory committee recommends approval of Tracleer for PAH*. DailyDrugNews.com (Daily Essentials) 2001, Aug 13.

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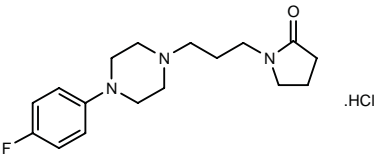
MONOGRAPH – Mealy, N.E. et al. *Bosentan*. Drugs Fut 2001, 26(12): 1149.

*Drug Data Rep 1994, 016(07): 0638.

CDRI-93/478*

296868

1-[3-[4-(4-Fluorophenyl)piperazin-1-yl]propyl]pyrrolidin-2-one hydrochloride



C17 H24 F N3 O . HCl; Mol wt: 341.8555

ACTION – Antiischemic and antihypertensive agent undergoing advanced-stage preclinical development, an arylpiperazine derivative that acts through blockade of peripheral α_1 -adrenoceptors.

SOURCES – Central Drug Research Institute, Lucknow (IN); Council of Scientific and Industrial Research, New Delhi (IN).

REFERENCES

1. Sinha, N. et al. (Council of Scientific and Industrial Research) *1-[4-Aryl]piperazin-1-yl]-3-[2-oxopyrrolidin/piperidin-1-yl]propanes and their use in medical treatments*. US 6150367.

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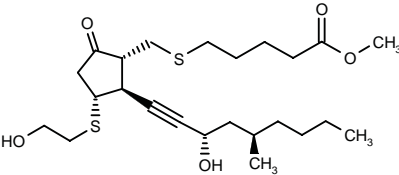
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*Identified compound **296868** Drug Data Rep 2001, 023(04): 0348.

TREATMENT OF DISORDERS OF THE CORONARY ARTERIES AND ATHEROSCLEROSIS

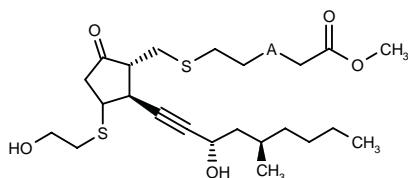
310675

11-Deoxy-11-(2-hydroxyethylsulfanyl)-17(R),20-dimethyl-13,14-didehydro-6-thiaprostaglandin E₁ methyl ester



C24 H40 O5 S2; Mol wt: 472.7070

ACTION – Prostaglandin E₁ analogue effective as an inhibitor of vascular smooth muscle cell proliferation, as demonstrated by complete inhibition of the proliferation of human aorta-derived vascular cells at 1 mM. Potentially useful in the treatment of post-PTCA restenosis. Other exemplified compounds are:



Compound	A	Isomer	Formula
310676	CH2	R	C ₂₄ H ₄₀ O ₅ S ₂
310677	S	S	C ₂₃ H ₃₈ O ₅ S ₃

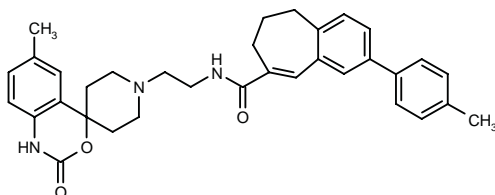
SOURCE – Taisho.

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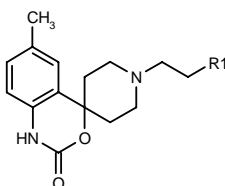
311519

N-[2-(6-Methyl-2-oxo-2,4-dihydro-1*H*-spiro[3,1-benzoxazine-4,4'-piperidin]-1'-yl)ethyl]-2-(4-methylphenyl)-6,7-dihydro-5*H*-benzocycloheptene-8-carboxamide



C34 H37 N3 O3; Mol wt: 535.6843

ACTION – Chemokine MCP-1 receptor (CCR2) antagonist proven to inhibit [¹²⁵I]-MCP-1 binding with an IC₅₀ of 0.031 μM. Potentially useful for the treatment of atherosclerosis, glomerulonephritis, pulmonary hypertension, rheumatism and asthma. Other exemplified spiro-[3,1-benzoxazine-4,4'-piperidine] compounds include the following:



Compound	R1	Formula
311520	7-(4-Me-Ph)-2,3-dihydro-1-benzoxepin-4-yl-CONH	C ₃₃ H ₃₅ N ₃ O ₄
311521	2-Me-5-(<i>t</i> -BuOCONH)-Ph	C ₂₇ H ₃₅ N ₃ O ₄
311522	2-Me-5-(cyclopentyl-OCONH)-Ph	C ₂₈ H ₃₅ N ₃ O ₄
311523	2-MeO-5-(<i>t</i> -BuOCONH)-Ph	C ₂₇ H ₃₅ N ₃ O ₅

SOURCE – Daiichi Pharmaceutical.

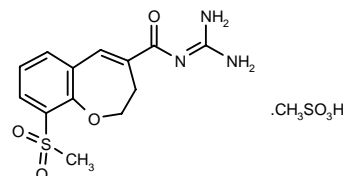
REFERENCES

1. Horino, H. et al. (Daiichi Pharmaceutical Co., Ltd.) *Benzoxazine derivs. and medicines containing them*. JP 2001278886.

FR-227369*

282621

N-(9-Methylsulfonyl-2,3-dihydro-1-benzoxepin-4-yl-carbonyl)guanidine methanesulfonate



C13 H15 N3 O4 S . C H4 O3 S; Mol wt: 405.4501

ACTION – Na⁺/H⁺ exchange inhibitor (IC₅₀ = 4.78 nM) potentially useful for the treatment of myocardial ischemia-reperfusion injury.

SOURCE – Fujisawa.

REFERENCES

1. Takenaka, K. et al. (Fujisawa Pharmaceutical Co., Ltd.) *Guanidine derivs*. EP 1073650, US 6346527, WO 9955690.

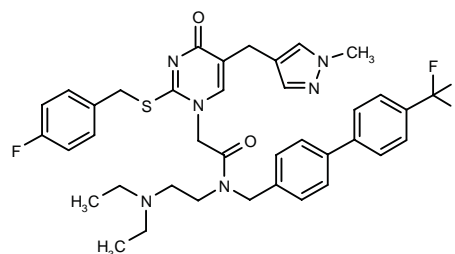
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*Identified compound **282621** (see **282620**) Drug Data Rep 2000, 022(02): 0145.

SB-435495*

296840

N-[2-(Diethylamino)ethyl]-2-[2-(4-fluorobenzylsulfanyl)-5-(1-methyl-1*H*-pyrazol-4-ylmethyl)-4-oxo-1,4-dihydropyrimidin-1-yl]-*N*-[4'-(trifluoromethyl)biphenyl-4-ylmethyl]-acetamide



C38 H40 F4 N6 O2 S; Mol wt: 720.8320

ACTION – An inhibitor of lipoprotein-associated phospholipase A₂ (Lp-PLA₂; IC₅₀ = 0.06 nM against recombinant human enzyme) with good activity in rabbit and human plasma (87 and 95% inhibition at 10 and 100 nM, respectively). Compound showed only a slight interaction with cytochrome P-450 3A4 (IC₅₀ = 10 μM) and exhibited good stability in human liver microsomes. In rabbits, it inhibited plasma Lp-PLA₂, with a maximum effect of about 70% at the dose of 10 mg/kg. Potentially useful for the treatment of atherosclerosis.

SOURCES – GlaxoSmithKline; Human Genome Sciences.

REFERENCES

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4. *GlaxoSmithKline updates R&D activities —merger makes way for robust pipeline.* DailyDrugNews.com (Daily Essentials) 2001, March 1.

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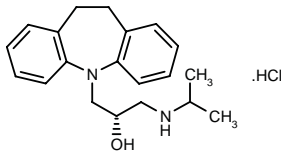
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*Identified compound **296840** (see **296831**) Drug Data Rep 2001, 023(04): 0350.

ANTIARRHYTHMIC DRUGS

311483

(–)-1-(10,11-Dihydro-5*H*-dibenzo[*b,f*]azepin-5-yl)-3-(iso-propylamino)propan-2(*S*)-ol hydrochloride



C20 H26 N2 O . HCl; Mol wt: 346.8993

ACTION – Antiarrhythmic agent with ventricular defibrillating activity, as measured in a cat model at doses as low as 0.5 mg/kg i.v. Compound also exhibited anti-fibrillatory activity, i.e., it elevated the fibrillation threshold potential (about 50% at 2 mg/kg). No changes in the ECG were seen after administration.

SOURCES – Scripps Research Institute, La Jolla, CA (US); Technion - Israel Institute of Technology, Haifa (IL); Tel Aviv University, Tel Aviv (IL).

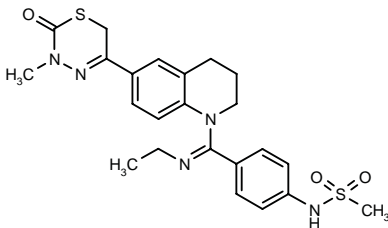
REFERENCES

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EMD-66398

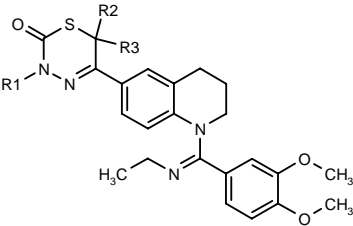
309746

N-[4-[1-(Ethylimino)-1-[6-(3-methyl-2-oxo-3,6-dihydro-2*H*-1,3,4-thiadiazin-5-yl)-1,2,3,4-tetrahydroquinolin-1-yl]-methyl]phenyl]methanesulfonamide



C23 H27 N5 O3 S2; Mol wt: 485.6303

ACTION – Selective class III antiarrhythmic agent proven to prolong the action potential duration in guinea pig myocytes at micromolar concentrations, as well as to inhibit in a concentration-dependent manner the K_{Vr} current in these cells, while having no effect on the slow delayed rectifier K⁺ current K_{Vs}, nor on the inward rectifier K⁺ current K_{IR}. In human myocytes, compound showed little or no effect on the transient and sustained outward K⁺ currents or L-type Ca²⁺ current. Other related compounds are:



Compound	R1	R2	R3	Formula
EMD-60417 [309741]	H	Me	Me	C ₂₅ H ₃₀ N ₄ O ₃ S
EMD-66430 [309744]	Me	H	H	C ₂₄ H ₂₈ N ₄ O ₃ S

SOURCE – Merck KGaA.

REFERENCES

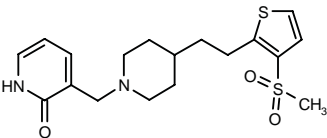
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2. Himmel, H.M. et al. *Three thiadiazinone derivatives, EMD 60417, EMD 66430, and EMD 66398, with class III antiarrhythmic activity but different electrophysiologic profiles.* J Cardiovasc Pharmacol 2001, 38(3): 438.

ER-129517

308631

3-[4-[2-[3-(Methylsulfonyl)thien-2-yl]ethyl]piperidin-1-ylmethyl]pyridin-2(1*H*)-one



C18 H24 N2 O3 S2; Mol wt: 380.5306

ACTION – Antiarrhythmic agent, a piperidine derivative with potent antifibrillatory activity in a canine vagotonic model, where it was found to prolong the atrial effective refractory period and terminate fibrillation more strongly than quinidine or dofetilide.

SOURCE – Eisai.

REFERENCES

1. Ozaki, F. et al. (Eisai Co., Ltd.) *Novel piperidine cpds. and drugs containing the same.* JP 2001270883, WO 0153288.

2. Tabata, M. et al. *Novel piperidine derivatives as anti-atrial fibrillation agent.* 21st Symp Med Chem (Nov 28-30, Kyoto) 2001, Abst 1P-13.

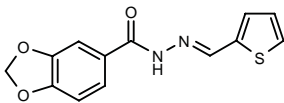
HEART FAILURE THERAPY

LASSBIO-294

311236

(E)-N'-(Thien-2-ylmethylene)-1,3-benzodioxole-5-carbohydrazide

L-294



C13 H10 N2 O3 S; Mol wt: 274.2990

ACTION – Cardiotonic agent, an inhibitor of cAMP-specific phosphodiesterase type 3 (PDE3) with positive inotropic effects in single fibers of frog skeletal muscle. Compound was also found to reduce fatigue development of skeletal muscle fibers and to accelerate recovery of maximal tetanic tension after fatigue developed. It increased in a concentration-dependent manner (5-50 μM) spontaneous contractions of isolated rat heart and exerted a positive inotropic effect in electrically stimulated cardiac tissue. In saponin-skinned ventricular cells, compound (100 μM) increased Ca²⁺ uptake into sarcoplasmic reticulum by 40% and induced a leftward shift in the caffeine dose–response curve when it was added to fibers during sarcoplasmic reticulum load. Other experiments demonstrated its ability to inhibit glutamate- or nitric oxide-induced neurotoxicity in rat cortical neurons. Potentially useful for the treatment of chronic heart failure, as well as for neuroprotection.

SOURCES – University of Maryland, Baltimore, MD (US); Universidade Federal do Rio de Janeiro, Rio de Janeiro (BR).

REFERENCES

1. Sudo, R.T. et al. (University of Maryland) *Thienylhydrazon with digitalis-like properties (positive inotropic effects)*. WO 0078754.

2. Castro, N.G. et al. *Protection of rat cortical neurons against glutamate and nitric oxide toxicity by LASSBio-294*. Soc Neurosci Abst 2001, 27: Abst 97.20.

3. Gonzalez-Serratos, H. et al. *A novel thienylhydrazone, (2-thienylidene)3,4-methylenedioxybenzoylhydrazine, increases inotropism and decreases fatigue of skeletal muscle*. J Pharmacol Exp Ther 2001, 299(2): 588.

4. Gonzalez-Serratos, H. et al. *The novel thienylhydrazone LASSBio-294 increases inotropism and decreases fatigue of skeletal muscle*. Soc Neurosci Abst 2001, 27: Abst 519.9.

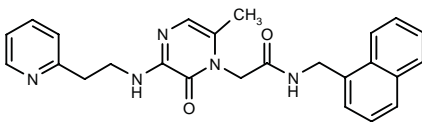
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AGENTS AFFECTING BLOOD COAGULATION

ANTICOAGULANTS

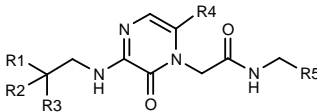
310781

2-[6-Methyl-2-oxo-3-[2-(2-pyridyl)ethylamino]-1,2-dihydropyrazin-1-yl]-N-(naphthalen-1-ylmethyl)acetamide



C25 H25 N5 O2; Mol wt: 427.5055

ACTION – Thrombin inhibitor, potentially useful for the prevention and treatment of venous thromboembolism, pulmonary embolism, deep vein thrombosis, thromboembolic stroke, atherosclerosis, thrombosis, reocclusion associated with percutaneous transluminal coronary angioplasty, occlusive cerebrovascular disease, as well as for maintaining vascular patency in a patient. Other specifically claimed heterocycle-containing acetamides include the following:



Compound	R1	R2=R3	R4	R5	Formula
310782	2-Pyr	H	Me	1-isoquinolyl	C ₂₄ H ₂₄ N ₆ O ₂
310783	2-Pyr	F	Me	1-NH2-4-isoquinoliny	C ₂₄ H ₂₃ F ₂ N ₇ O ₂
310784	2-Pyr	F	Cl	1,6-naphthyridin-8-yl	C ₂₂ H ₁₈ ClF ₂ N ₇ O ₂
310785	2-Pyr	H	Me	8-isoquinoliny	C ₂₄ H ₂₄ N ₆ O ₂
310786	2-Pyr	F	Me	8-quinolyl	C ₂₄ H ₂₂ F ₂ N ₆ O ₂
310787	Ph	H	Cl	1,6-naphthyridin-8-yl	C ₂₃ H ₂₁ ClN ₆ O ₂
310791	2-Pyr	F	Cl	1,2,3,4-tetrahydro-1,6-naphthyridin-8-yl	C ₂₂ H ₂₂ ClF ₂ N ₇ O ₂
310793	3-MeO-Ph	F	Cl	1,6-naphthyridin-8-yl	C ₂₄ H ₂₁ ClF ₂ N ₆ O ₃

SOURCE – Merck & Co.

REFERENCES

1. Barrow, J.C. et al. (Merck & Co., Inc.) *Thrombin inhibitors*. WO 0170229.

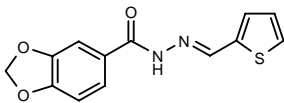
HEART FAILURE THERAPY

LASSBIO-294

311236

(E)-N'-(Thien-2-ylmethylene)-1,3-benzodioxole-5-carbohydrazide

L-294



C13 H10 N2 O3 S; Mol wt: 274.2990

ACTION – Cardiotonic agent, an inhibitor of cAMP-specific phosphodiesterase type 3 (PDE3) with positive inotropic effects in single fibers of frog skeletal muscle. Compound was also found to reduce fatigue development of skeletal muscle fibers and to accelerate recovery of maximal tetanic tension after fatigue developed. It increased in a concentration-dependent manner (5-50 μM) spontaneous contractions of isolated rat heart and exerted a positive inotropic effect in electrically stimulated cardiac tissue. In saponin-skinned ventricular cells, compound (100 μM) increased Ca²⁺ uptake into sarcoplasmic reticulum by 40% and induced a leftward shift in the caffeine dose–response curve when it was added to fibers during sarcoplasmic reticulum load. Other experiments demonstrated its ability to inhibit glutamate- or nitric oxide-induced neurotoxicity in rat cortical neurons. Potentially useful for the treatment of chronic heart failure, as well as for neuroprotection.

SOURCES – University of Maryland, Baltimore, MD (US); Universidade Federal do Rio de Janeiro, Rio de Janeiro (BR).

REFERENCES

1. Sudo, R.T. et al. (University of Maryland) *Thienylhydrazon with digitalis-like properties (positive inotropic effects)*. WO 0078754.

2. Castro, N.G. et al. *Protection of rat cortical neurons against glutamate and nitric oxide toxicity by LASSBio-294*. Soc Neurosci Abst 2001, 27: Abst 97.20.

3. Gonzalez-Serratos, H. et al. *A novel thienylhydrazone, (2-thienylidene)3,4-methylenedioxybenzoylhydrazine, increases inotropism and decreases fatigue of skeletal muscle*. J Pharmacol Exp Ther 2001, 299(2): 588.

4. Gonzalez-Serratos, H. et al. *The novel thienylhydrazone LASSBio-294 increases inotropism and decreases fatigue of skeletal muscle*. Soc Neurosci Abst 2001, 27: Abst 519.9.

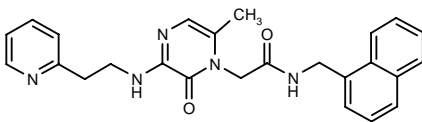
5. Sudo, R.T. et al. *The new compound, LASSBio 294, increases the contractility of intact and saponin-skinned cardiac muscle from Wistar rats*. Br J Pharmacol 2001, 134(3): 603.

AGENTS AFFECTING BLOOD COAGULATION

ANTICOAGULANTS

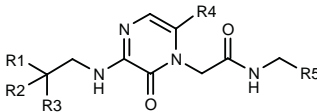
310781

2-[6-Methyl-2-oxo-3-[2-(2-pyridyl)ethylamino]-1,2-dihydropyrazin-1-yl]-N-(naphthalen-1-ylmethyl)acetamide



C25 H25 N5 O2; Mol wt: 427.5055

ACTION – Thrombin inhibitor, potentially useful for the prevention and treatment of venous thromboembolism, pulmonary embolism, deep vein thrombosis, thromboembolic stroke, atherosclerosis, thrombosis, reocclusion associated with percutaneous transluminal coronary angioplasty, occlusive cerebrovascular disease, as well as for maintaining vascular patency in a patient. Other specifically claimed heterocycle-containing acetamides include the following:



Compound	R1	R2=R3	R4	R5	Formula
310782	2-Pyr	H	Me	1-isoquinolyl	C ₂₄ H ₂₄ N ₆ O ₂
310783	2-Pyr	F	Me	1-NH2-4-isoquinoliny	C ₂₄ H ₂₃ F ₂ N ₇ O ₂
310784	2-Pyr	F	Cl	1,6-naphthyridin-8-yl	C ₂₂ H ₁₈ ClF ₂ N ₇ O ₂
310785	2-Pyr	H	Me	8-isoquinoliny	C ₂₄ H ₂₄ N ₆ O ₂
310786	2-Pyr	F	Me	8-quinolyl	C ₂₄ H ₂₂ F ₂ N ₆ O ₂
310787	Ph	H	Cl	1,6-naphthyridin-8-yl	C ₂₃ H ₂₁ ClN ₆ O ₂
310791	2-Pyr	F	Cl	1,2,3,4-tetrahydro-1,6-naphthyridin-8-yl	C ₂₂ H ₂₂ ClF ₂ N ₇ O ₂
310793	3-MeO-Ph	F	Cl	1,6-naphthyridin-8-yl	C ₂₄ H ₂₁ ClF ₂ N ₆ O ₃

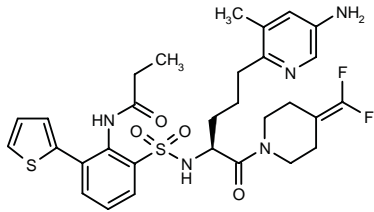
SOURCE – Merck & Co.

REFERENCES

1. Barrow, J.C. et al. (Merck & Co., Inc.) *Thrombin inhibitors*. WO 0170229.

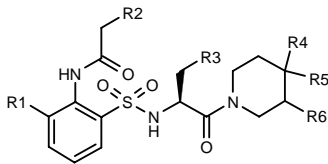
310810

N-[2-[*N*-[4-(5-Amino-3-methylpyridin-2-yl)-1 (*S*)-[4-(di-fluoromethylene)piperidin-1-ylcarbonyl]butyl]sulfamoyl]-6-(2-thienyl)phenyl]propionamide



C30 H35 F2 N5 O4 S2; Mol wt: 631.7655

ACTION – Anticoagulant that acts as a thrombin inhibitor. Other specifically claimed compounds from this series of pyridine- and benzenesulfonamides are:



Compound	R1	R2	R3	R4	R5	R6	Formula
310811	3-F-Ph	H	5-NH2-2-Pyr-CH2CH2	-CF2-	H		C ₃₀ H ₃₂ F ₃ N ₅ O ₄ S
310812	cyclopentyl	Me	6-NH2-3-Pyr-CH2CH2	H	H	H	C ₂₉ H ₄₁ N ₅ O ₄ S
310813	2-thienyl	H	6-NH2-3-Pyr-CH2CH2	-CF2-	H		C ₂₈ H ₃₁ F ₂ N ₅ O ₄ S ₂
310814	2-thienyl	Me	6-NH2-3-Pyr-CH2CH2	CF3	bond		C ₂₉ H ₃₂ F ₃ N ₅ O ₄ S ₂
310816	cyclopentyl	Me	6-NH2-4-Me-3-Pyr-CH2CH2	-CF2-	H		C ₃₁ H ₄₁ F ₂ N ₅ O ₄ S
310817	cyclopentyl	H	6-NH2-2-Pyr-CH2CH2	Me	H	H	C ₂₉ H ₄₁ N ₅ O ₄ S
310819	3-F-Ph	H	5-NH2-2-Pyr-CH2CH2	Me	H	H	C ₃₀ H ₃₆ FN ₅ O ₄ S
310820	Ph	H	(<i>Z</i>)-5-NH2-2-Pyr-CH=CH	Me	H	H	C ₃₀ H ₃₅ N ₅ O ₄ S

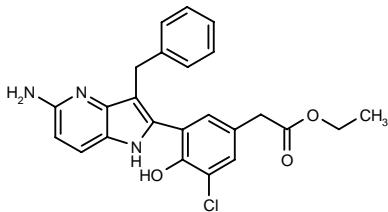
SOURCE – Sanofi-Synthélabo.

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1. Altenburger, J.-M. et al. (Sanofi-Synthélabo) *N*-(Heterocycl)yl)benzene or pyridine sulphonamides as antithrombotic agents and anticoagulants. WO 0170736.

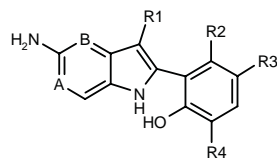
310841

2-[3-(5-Amino-3-benzyl-1*H*-pyrrolo[3,2-*b*]pyridin-2-yl)-5-chloro-4-hydroxyphenyl]acetic acid ethyl ester



C24 H22 Cl N3 O3; Mol wt: 435.9088

ACTION – Anticoagulant that acts as a factor Xa, factor VIIa and/or thrombin inhibitor, and is thus potentially useful for the treatment of thromboembolic disorders including unstable angina, ischemic attacks, stroke, atherosclerosis, venous thrombosis, deep vein thrombosis, thrombophlebitis and arterial, kidney and pulmonary embolism. Other specifically claimed compounds are:



Compound	R1	R2	R3	R4	A	B	Formula
310843	CH2Ph		-CO(CH2)3-	Br	CH	N	C ₂₄ H ₂₀ BrN ₃ O ₂
310844	CH2Ph	H	CH2CO2H	3-NO2-Ph	CH	N	C ₂₈ H ₂₂ N ₄ O ₅
310846	CH2Ph	H	CH2CONH2	Cl	CH	N	C ₂₂ H ₁₉ ClN ₄ O ₂
310847	H	H	Cl	Cl	N	CH	C ₁₃ H ₉ Cl ₂ N ₃ O
310848	CH2Ph	H	CH2CH2CO2H	Cl	CH	N	C ₂₃ H ₂₀ ClN ₃ O ₃
310850	H	H	CH2CO2H	Cl	CH	N	C ₁₅ H ₁₂ ClN ₃ O ₃
310851	H	H	4-morpholinyl-CH2CH2NHCOCH2	3-NO2-Ph	CH	N	C ₂₇ H ₂₈ N ₆ O ₅
310852	H	H	CH2CONH-CH2CH2N(Me)2	3-NO2-Ph	CH	N	C ₂₅ H ₂₆ N ₆ O ₄

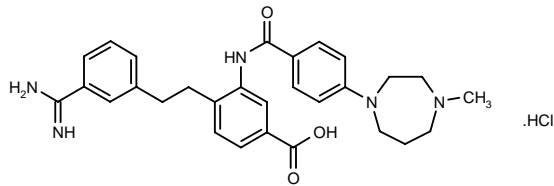
SOURCE – Celera Genomics.

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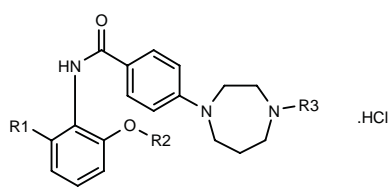
311439

4-[2-(3-Amidinophenyl)ethyl]-3-[4-(4-methylperhydro-1,4-diazepin-1-yl)benzamido]benzoic acid hydrochloride



C29 H33 N5 O3 . HCl; Mol wt: 536.0726

ACTION – Anticoagulant, a factor Xa inhibitor with a CT₂ value (concentration required to double coagulation time) of 0.10 μM when tested in human plasma treated with human factor Xa. Potentially useful for the treatment of stroke, cerebral thrombosis and embolism, transient cerebral ischemic attack, myocardial infarction, unstable angina pectoris, coronary thrombolysis, pulmonary infarction and embolism, peripheral arterial obstruction, deep vein thrombosis, postoperative thrombus formation, post-PTCA restenosis, etc. Other exemplified diazepane derivatives include the following:



Compound	R1	R2	R3	Formula
311440	4-MeO-PhNHCO	H	Me	C ₂₇ H ₃₀ N ₄ O ₄ .HCl
311441	4-F-PhNHCO	H	Me	C ₂₆ H ₂₇ FN ₄ O ₃ .HCl
311442	4-MeO-PhCONH	H	4-Pyr	C ₃₁ H ₃₁ N ₅ O ₄ .HCl
311443	4-MeO-PhCONH	CH ₂ CH ₂ OH	Me	C ₂₉ H ₃₄ N ₄ O ₅ .HCl

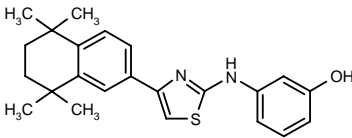
SOURCE – Yamanouchi.

REFERENCES

1. Hirayama, F. et al. (Yamanouchi Pharmaceutical Co., Ltd.) *Diazepane derivs. or salts thereof*. WO 0174791.

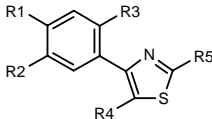
311534

3-[4-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)thiazol-2-ylamino]phenol



C23 H26 N2 O S; Mol wt: 378.5374

ACTION – An inhibitor of plasminogen activator inhibitor-1 (PAI-1), potentially useful for the treatment of thrombosis, myocardial and pulmonary infarction, intraatrial thrombus in atrial fibrillation, deep vein thrombosis, disseminated intravascular coagulation syndrome, diabetic complications, restenosis and stroke. Other specifically claimed substituted thiazole derivatives include the following:



Compound	R1	R2	R3	R4	R5	Formula
311536	-C(Me)2CH2CH2C(Me)2-		Et	H	3-CO2HPhNH	C ₂₆ H ₃₀ N ₂ O ₂ S
311537	Br	H	H	H	3-Cl-PhNH	C ₁₅ H ₁₀ BrClN ₂ S
311538	Br	H	H	H	4-CN-PhNH	C ₁₆ H ₁₀ BrN ₃ S
311539	CF ₃	H	H	H	4-NO ₂ -PhNH	C ₁₆ H ₁₀ F ₃ N ₂ O ₂ S
311540	F	F	H	H	3-CF ₃ -PhNH	C ₁₆ H ₉ F ₃ N ₂ S
311541	Cl	H	H	4-Me-Ph	4-NH ₂ -PhNH	C ₂₂ H ₁₈ ClN ₃ S
311545	NO ₂	H	H	H	4-(PhCH ₂ O)-PhNH	C ₂₂ H ₁₇ N ₃ O ₃ S
311546	-C(Me)2CH2CH2C(Me)2-		H	H	CH ₂ CN	C ₁₉ H ₂₂ N ₂ S

SOURCE – 3-Dimensional Pharmaceuticals.

REFERENCES

1. Dhanoa, D.S. et al. (3-Dimensional Pharmaceuticals, Inc.) *Substd. thiazoles and the use thereof as inhibitors of plasminogen activator inhibitor-1*. WO 0174793.

CEPROTIN™

305825

Monoclonal antibody-purified, double viral-inactivated human protein C concentrate

ACTION – Highly purified human plasma protein C concentrate.

INDICATION – Treatment of purpura fulminans and coumarin-induced skin necrosis in patients with severe congenital protein C deficiency; short-term prophylaxis in patients with severe congenital protein C deficiency.

PRESENTATION – Vials containing powder and solvent for solution for injection, 500 IU and 1000 IU (100 IU/ml human protein C when reconstituted).

PROPRIETARY NAME – *Ceprotin* (EU).

SOURCE – Baxter.

REFERENCES

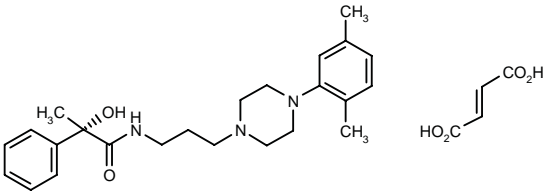
- 1. Berntorp, E. et al. *An approach to study the viral safety of plasma-derived products in previously treated, non-infected patients*. Haemophilia 2001, 7(4): 360.
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- 3. *Baxter receives EMEA approval for Ceprotin*. DailyDrugNews.com (Daily Essentials), July 19.
- 4. *Replacement therapy for congenital protein C deficiency now available in Europe*. DailyDrugNews.com (Daily Essentials) 2001, Dec 14.

RENAL–UROLOGIC DRUGS

BENIGN PROSTATIC HYPERPLASIA THERAPY

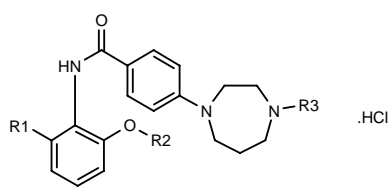
310289

(+)-*N*-[3-[4-(2,5-Dimethylphenyl)piperazin-1-yl]propyl]-2(*S*)-hydroxy-2-phenylpropionamide fumarate



C24 H33 N3 O2 . C4 H4 O4; Mol wt: 511.6153

ACTION – A representative compound from a series of phenylpiperazine derivatives with high affinity for α_1 -adrenoceptors (K_i = 13 nM against [³H]-prazosin binding in rat cerebral cortex preparations). In functional assays, compound exhibited a pK_b value of 8.3 against phenyl-ephrine-induced contractions of rabbit prostatic urethra and was found to exhibit selectivity for portal vein tissue relative to aortic tissue in both rat (K_b = 1.4 nM vs. 45 nM) and rabbit preparations (K_b = 1.6 nM vs. 63 nM). Claimed for the treatment of benign prostatic hyperplasia, portal hypertension and cirrhosis.



Compound	R1	R2	R3	Formula
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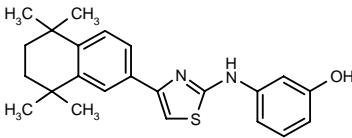
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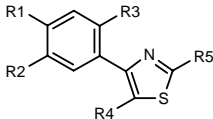
311534

3-[4-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)thiazol-2-ylamino]phenol



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311538	Br	H	H	H	4-CN-PhNH	C ₁₆ H ₁₀ BrN ₃ S
311539	CF ₃	H	H	H	4-NO ₂ -PhNH	C ₁₆ H ₁₀ F ₃ N ₂ O ₂ S
311540	F	F	H	H	3-CF ₃ -PhNH	C ₁₆ H ₉ F ₃ N ₂ S
311541	Cl	H	H	4-Me-Ph	4-NH ₂ -PhNH	C ₂₂ H ₁₈ ClN ₃ S
311545	NO ₂	H	H	H	4-(PhCH ₂ O)- -PhNH	C ₂₂ H ₁₇ N ₃ O ₃ S
311546	-C(Me)2CH2CH2C(Me)2-		H	H	CH ₂ CN	C ₁₉ H ₂₂ N ₂ S

SOURCE – 3-Dimensional Pharmaceuticals.

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PROPRIETARY NAME – *Ceprotin* (EU).

SOURCE – Baxter.

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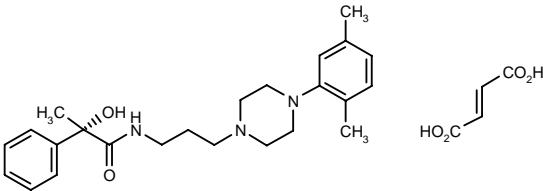
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- 2. Rogy, S. et al. *The efficacy and safety of Ceprotin, a highly purified protein C concentrate, in the treatment of purpura fulminans and coumarin-induced skin necrosis in patients with protein C deficiency*. Thromb Haemost 2001, (Suppl.): Abst P1422.
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RENAL–UROLOGIC DRUGS

BENIGN PROSTATIC HYPERPLASIA THERAPY

310289

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SOURCE – SCRAS.

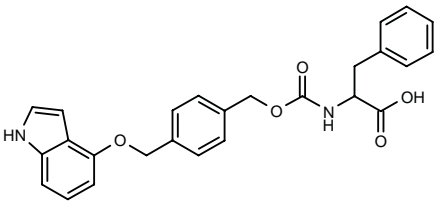
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TREATMENT OF URINARY INCONTINENCE

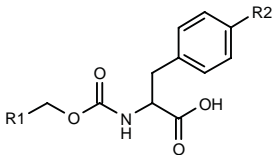
310468

N-[4-(1*H*-Indol-4-yloxymethyl)benzyloxycarbonyl]-DL-phenylalanine



C26 H24 N2 O5; Mol wt: 444.4846

ACTION – Prostaglandin (PGI₂) IP receptor antagonist (pK_i = 8.7), expected to be useful for the treatment of bladder disorders associated with bladder outlet obstruction and urinary incontinence, pain, inflammation (particularly inflammation arising from microbial infection, arthritis, bladder inflammation, urethritis, prostatitis and conjunctivitis), asthma, edema formation and hypotension associated with septic shock. Other exemplified carbamic acid derivatives include the following:



Compound	R1	R2	Isomer	Formula
310469	4-(PhOCH2)-Ph	H	R	C ₂₄ H ₂₃ NO ₅
310470	5-Ph-2-benzoxazolyl	H	R	C ₂₄ H ₂₀ N ₂ O ₅
310471	5-(1,3-benzodioxol-5-yl)-2-benzofuryl	F	R	C ₂₆ H ₂₀ FNO ₇
310472	4-(4-indolyl-OCH2)-Ph	H		C ₂₆ H ₂₄ N ₂ O ₅

SOURCE – Roche.

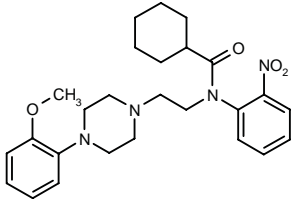
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REC-15/3079*

273181

N-[2-[4-(2-Methoxyphenyl)piperazin-1-yl]ethyl]-N-(2-nitrophenyl)cyclohexanecarboxamide



C26 H34 N4 O4; Mol wt: 466.5786

ACTION – Pre- and postsynaptic 5-HT_{1A} receptor antagonist with high affinity for native (K_i = 0.7 nM in rat hippocampus) and human recombinant (K_i = 0.2 nM) 5-HT_{1A} receptors, and selectivity versus a panel of receptors and binding sites. In *in vitro* functional assays, it acted as a competitive antagonist (pK_b = 10.5), and *in vivo* it antagonized 8-OH-DPAT-induced hypothermia in mice (presynaptic 5-HT_{1A} receptor-mediated response; ID₅₀ = 20 µg/kg i.v.) and forepaw treading in rats (postsynaptic 5-HT_{1A}-mediated response; ID₅₀ = 36 µg/kg i.v.). It displayed poor activity *in vitro* in antagonizing bladder and urethral contractions induced by carbachol and noradrenaline (pK_b = 5-6), but in anesthetized rats (10-100 µg/kg i.v.) it blocked isovolumic bladder contractions and in conscious rats and guinea pigs (300-1000 µg/kg i.v.) it increased bladder volume capacity without affecting bladder contractility. No sedative, analgesic, anxiolytic or antidepressant effects were seen at doses at least 10-fold higher than those effective on the bladder. Potentially useful for the treatment of micturition disorders such as urinary incontinence.

SOURCE – Recordati.

REFERENCES

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3. *New treatment for urinary incontinence in the Recordati pipeline*. DailyDrugNews.com (Daily Essentials) 1999, Aug 31.

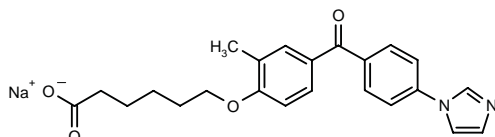
4. *REC 15/3079 development status*. Recordati Company Communication 2000, May 17.

*Identified compound 273181 Drug Data Rep 1999, 021(04): 0326.

TREATMENT OF RENAL DISEASES

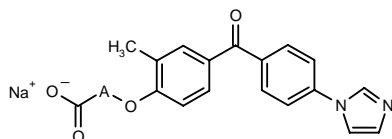
310925

6-[4-[4-(1*H*-Imidazol-1-yl)benzoyl]-2-methylphenoxy]-hexanoic acid sodium salt



C23 H23 N2 Na O4; Mol wt: 414.4347

ACTION – Agent with the ability to inhibit the production of the arachidonic acid metabolite 20-hydroxyeicosatetraenoic acid (20-HETE), as demonstrated in hypertensive rat kidney preparations ($IC_{50} = 7.9$ nM). Potentially useful for the treatment of various circulatory organ diseases, particularly nephropathies and cerebrovascular diseases. Other exemplified imidazole-substituted benzo-phenones include the following:



Compound	A	Formula
310926	-(CH2)10-	C ₂₈ H ₃₃ N ₂ NaO ₄
310927	-(CH2)4-	C ₂₂ H ₂₁ N ₂ NaO ₄
310928	-(CH2)3-	C ₂₁ H ₁₉ N ₂ NaO ₄

SOURCE – Taisho.

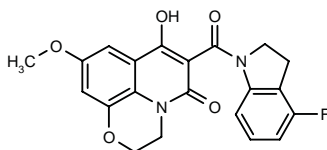
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FR-149470

311254

6-(4-Fluoro-2,3-dihydro-1*H*-indol-1-ylcarbonyl)-7-hydroxy-9-methoxy-3,5-dihydro-2*H*-[1,4]oxazino[2,3,4-*ij*]quinolin-5-one



C21 H17 F N2 O5; Mol wt: 396.3723

ACTION – Immunomodulator, a linomide derivative with potent and specific activity in a chronic graft-versus-host disease model of lupus nephritis. Compound exhibited an improved safety profile compared to the parent compound, good bioavailability and water solubility.

SOURCE – Fujisawa.

REFERENCES

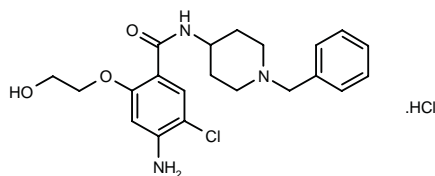
1. Spears, G. et al. *The discovery of the novel immunomodulator FR149470.* 21st Symp Med Chem (Nov 28-30, Kyoto) 2001, Abst 2P-29.

GASTROINTESTINAL DRUGS

TREATMENT OF ESOPHAGEAL DISEASES

310273

4-Amino-*N*-(1-benzylpiperidin-4-yl)-5-chloro-2-(2-hydroxyethoxy)benzamide hydrochloride



C21 H26 Cl N3 O3 . HCl; Mol wt: 440.3683

ACTION – Dopamine D2 receptor antagonist and 5-HT₄ receptor agonist that displayed a K_i of 2.3 nM against dopamine D2 receptors in membranes of rat corpus striatum, and inhibited the carbachol-induced contraction of rat esophageal sphincters with an ED_{50} of 160 nM. It demonstrated a gastric motility-promoting effect following oral administration to rats (3-30 mg/kg) and was effective against apomorphine-induced emesis when orally administered to dogs ($ED_{80} = 0.23$ mg/kg). In acute toxicity studies in rats, this compound gave an LD_{50} value of 1414 mg/kg p.o. Potentially useful for the treatment of reflux esophagitis, unidentified epigastric complaints, gastritis, gastric ulcer and related diseases.

SOURCE – Kissei.

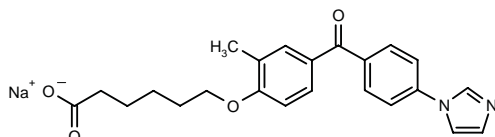
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TREATMENT OF RENAL DISEASES

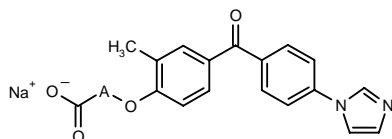
310925

6-[4-[4-(1*H*-Imidazol-1-yl)benzoyl]-2-methylphenoxy]-hexanoic acid sodium salt



C₂₃ H₂₃ N₂ Na O₄; Mol wt: 414.4347

ACTION – Agent with the ability to inhibit the production of the arachidonic acid metabolite 20-hydroxyeicosatetraenoic acid (20-HETE), as demonstrated in hypertensive rat kidney preparations (IC₅₀ = 7.9 nM). Potentially useful for the treatment of various circulatory organ diseases, particularly nephropathies and cerebrovascular diseases. Other exemplified imidazole-substituted benzo-phenones include the following:



Compound	A	Formula
310926	-(CH ₂) ₁₀ -	C ₂₈ H ₃₃ N ₂ NaO ₄
310927	-(CH ₂) ₄ -	C ₂₂ H ₂₁ N ₂ NaO ₄
310928	-(CH ₂) ₃ -	C ₂₁ H ₁₉ N ₂ NaO ₄

SOURCE – Taisho.

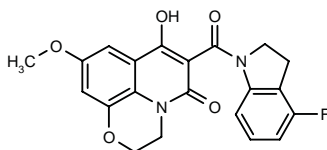
REFERENCES

1. Sato, M. et al. (Taisho Pharmaceutical Co., Ltd.) *Imidazolylbenzophenone derivs.* WO 0168610.

FR-149470

311254

6-(4-Fluoro-2,3-dihydro-1*H*-indol-1-ylcarbonyl)-7-hydroxy-9-methoxy-3,5-dihydro-2*H*-[1,4]oxazino[2,3,4-*ij*]quinolin-5-one



C₂₁ H₁₇ F N₂ O₅; Mol wt: 396.3723

ACTION – Immunomodulator, a linomide derivative with potent and specific activity in a chronic graft-versus-host disease model of lupus nephritis. Compound exhibited an improved safety profile compared to the parent compound, good bioavailability and water solubility.

SOURCE – Fujisawa.

REFERENCES

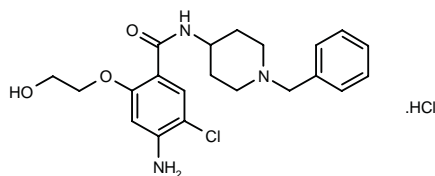
1. Spears, G. et al. *The discovery of the novel immunomodulator FR149470.* 21st Symp Med Chem (Nov 28-30, Kyoto) 2001, Abst 2P-29.

GASTROINTESTINAL DRUGS

TREATMENT OF ESOPHAGEAL DISEASES

310273

4-Amino-*N*-(1-benzylpiperidin-4-yl)-5-chloro-2-(2-hydroxyethoxy)benzamide hydrochloride



C₂₁ H₂₆ Cl N₃ O₃ . HCl; Mol wt: 440.3683

ACTION – Dopamine D₂ receptor antagonist and 5-HT₄ receptor agonist that displayed a K_i of 2.3 nM against dopamine D₂ receptors in membranes of rat corpus striatum, and inhibited the carbachol-induced contraction of rat esophageal sphincters with an ED₅₀ of 160 nM. It demonstrated a gastric motility-promoting effect following oral administration to rats (3-30 mg/kg) and was effective against apomorphine-induced emesis when orally administered to dogs (ED₈₀ = 0.23 mg/kg). In acute toxicity studies in rats, this compound gave an LD₅₀ value of 1414 mg/kg p.o. Potentially useful for the treatment of reflux esophagitis, unidentified epigastric complaints, gastritis, gastric ulcer and related diseases.

SOURCE – Kissei.

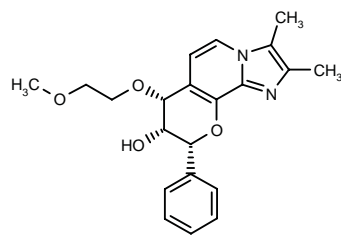
REFERENCES

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ANTIULCER DRUGS

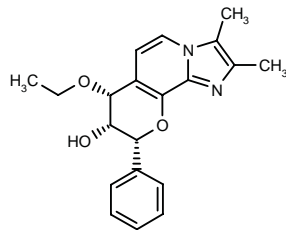
311068

7(R)-(2-Methoxyethoxy)-2,3-dimethyl-9(R)-phenyl-8,9-dihydro-7H-imidazo[1,2-a]pyrano[2,3-c]pyridin-8(R)-ol



C21 H24 N2 O4; Mol wt: 368.4306

ACTION – Gastric antisecretory agent for use in the treatment of gastrointestinal inflammatory diseases and lesions including ulcers, gastritis, reflux esophagitis, Zollinger-Ellison syndrome and hyperacidic or medicament-related functional gastropathy. Following i.v. administration to rats, compound was able to completely inhibit gastric acid secretion at 1 μmol/kg. Another exemplified imidazopyridine derivative is:



311069: C20 H22 N2 O3

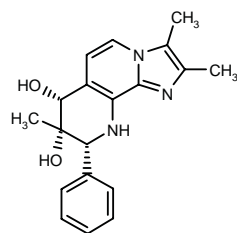
SOURCE – Byk Gulden.

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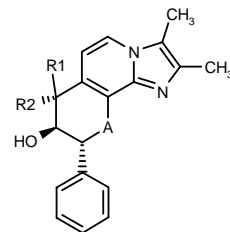
311071

2,3,8(S)-Trimethyl-9(R)-phenyl-7,8,9,10-tetrahydroimidazo[1,2-h]-1,7-naphthyridine-7(R),8-diol



C19 H21 N3 O2; Mol wt: 323.3939

ACTION – Gastric antisecretory agent for use in the treatment of gastrointestinal inflammatory diseases and lesions including ulcers, gastritis, reflux esophagitis, Zollinger-Ellison syndrome and hyperacidic or medicament-related functional gastropathy. Following i.v. administration to rats, compound was able to completely inhibit gastric acid secretion at 1 μmol/kg. Other exemplified alkylated imidazopyridine derivative are:



Compound	R1	R2	A	Formula
311072	Me	OH	NH	C ₁₉ H ₂₁ N ₃ O ₂
311074	-CH2-		NH	C ₁₉ H ₁₉ N ₃ O
311075	Me	OH	O	C ₁₉ H ₂₀ N ₂ O ₃

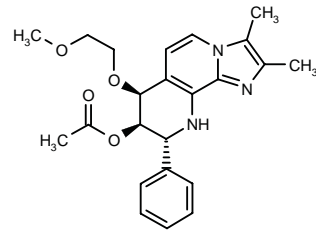
SOURCE – Byk Gulden.

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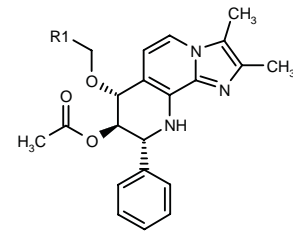
311081

Acetic acid 7(S)-(2-methoxyethoxy)-2,3-dimethyl-9(R)-phenyl-7,8,9,10-tetrahydroimidazo[1,2-h]-1,7-naphthyridin-8(R)-yl ester



C23 H27 N3 O4; Mol wt: 409.4833

ACTION – Gastric antisecretory agent for use in the treatment of gastrointestinal inflammatory diseases and lesions including ulcers, gastritis, reflux esophagitis, Zollinger-Ellison syndrome and hyperacidic or medication-related functional gastropathy. Following i.v. administration to rats, compound was able to completely inhibit gastric acid secretion at 3 μmol/kg. Other exemplified imidazopyridine derivatives are:



Compound	R1	Formula
311083	CH2OMe	C ₂₃ H ₂₇ N ₃ O ₄
311085	H	C ₂₁ H ₂₃ N ₃ O ₃

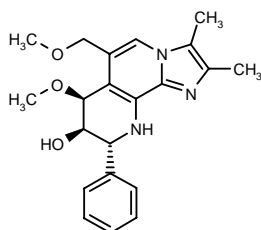
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REFERENCES

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311086

7-(*S*)-Methoxy-6-(methoxymethyl)-2,3-dimethyl-9(*R*)-phenyl-7,8,9,10-tetrahydroimidazo[1,2-*h*]-1,7-naphthyridin-8(*R*)-ol



C21 H25 N3 O3; Mol wt: 367.4465

ACTION – Gastric antisecretory agent for use in the treatment of gastrointestinal inflammatory diseases and lesions including ulcers, gastritis, reflux esophagitis, Zollinger-Ellison syndrome and hyperacidic or medication-related functional gastropathy. Following i.v. administration to rats, compound was able to completely inhibit gastric acid secretion at 3 µmol/kg.

SOURCE – Byk Gulden.

REFERENCES

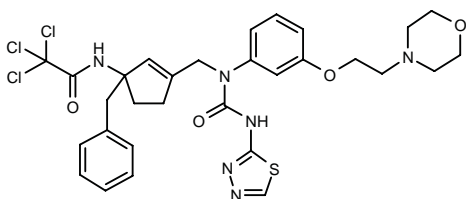
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AGENTS FOR IRRITABLE BOWEL SYNDROME

310513

N-[1-Benzyl-3-[1-[3-[2-(4-morpholinyl)ethoxy]phenyl]-3-(1,3,4-thiadiazol-2-yl)ureidomethyl]-2-cyclopenten-1-yl]-2,2,2-trichloroacetamide

N-[3-Benzyl-3-(trichloroacetamido)-1-cyclopenten-1-ylmethyl]-*N*-[3-[2-(4-morpholinyl)ethoxy]phenyl]-*N'*-(1,3,4-thiadiazol-2-yl)urea



C30 H33 Cl3 N6 O4 S; Mol wt: 680.0537

ACTION – Motilin receptor antagonist found to inhibit [¹²⁵I]-motilin binding to motilin receptors in rabbit colon by 17% at 100 nM. Potentially useful for the treatment of irritable bowel syndrome and esophageal reflux.

SOURCE – Ortho-McNeil.

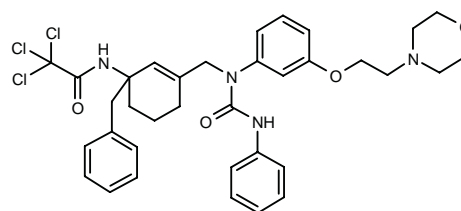
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1. Chen, R.H. and Xiang, M.A. (Ortho-McNeil Pharmaceutical, Inc.) *Novel cyclopentene derivs. useful as antagonists of the motilin receptor.* WO 0168620.

310514

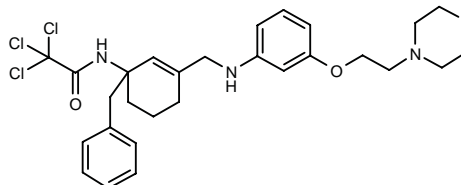
N-[1-Benzyl-3-[1-[3-[2-(4-morpholinyl)ethoxy]phenyl]-3-phenylureidomethyl]-2-cyclohexen-1-yl]-2,2,2-trichloroacetamide

N-[3-Benzyl-3-(trichloroacetamido)-1-cyclohexen-1-ylmethyl]-*N*-[3-[2(4-morpholinyl)ethoxy]phenyl]-*N'*-phenylurea



C35 H39 Cl3 N4 O4; Mol wt: 686.0761

ACTION – Motilin receptor antagonist found to inhibit [¹²⁵I]-motilin binding to motilin receptors in rabbit colon by 62% at 50 nM. Potentially useful for the treatment of irritable bowel syndrome and esophageal reflux. Another exemplified cyclohexene derivative is:



310515: C28 H34 Cl3 N3 O3

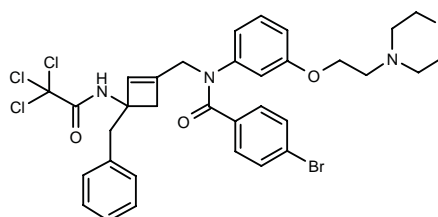
SOURCE – Ortho-McNeil.

REFERENCES

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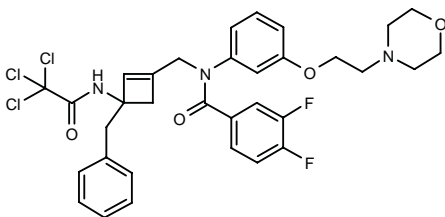
310516

N-[3-Benzyl-3-(2,2,2-trichloroacetamido)-1-cyclobuten-1-ylmethyl]-4-bromo-*N*-[3-[2-(4-morpholinyl)ethoxy]phenyl]benzamide



C33 H33 Br Cl3 N3 O4; Mol wt: 721.9037

ACTION – Motilin receptor antagonist found to inhibit [¹²⁵I]-motilin binding to motilin receptors in rabbit colon by 47% at 10,000 nM. Potentially useful for the treatment of irritable bowel syndrome and esophageal reflux. Another cyclobutene derivative is:



310517: C33 H32 Cl3 F2 N3 O4

SOURCE – Novo Nordisk.

REFERENCES

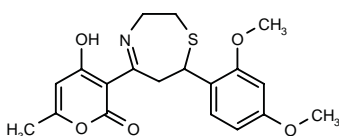
1. Chen, R.H. and Xiang, M.A. (Ortho-McNeil Pharmaceutical, Inc.) *Novel cyclobutene derivs. useful as antagonists of the motilin receptor*. WO 0168622.

AGENTS FOR INFLAMMATORY BOWEL DISEASE

KF-38789

297683

3-[7-(2,4-Dimethoxyphenyl)-2,3,6,7-tetrahydro-1,4-thiazepin-5-yl]-4-hydroxy-6-methyl-2H-pyran-2-one



C19 H21 N O5 S; Mol wt: 375.4429

ACTION – Potent and selective noncarbohydrate inhibitor of P-selectin with an IC₅₀ of 1.97 μM for inhibition of U-937 cell binding to immobilized P-selectin-Ig and inactive against E-selectin-Ig- and L-selectin-Ig-mediated cell adhesion. Compound was also found to inhibit P-selectin-induced superoxide production from human polymorphonuclear cells (PMNs) in a concentration-dependent fashion (0.1-10 μM), giving about 40% inhibition at the highest concentration. *In vivo* in a mouse model of thioglycollate-induced peritonitis, compound at a dose of 1 mg/kg i.v. significantly reduced leukocyte accumulation in the peritoneal cavity. Potentially useful for the treatment of P-selectin-mediated inflammatory disorders.

SOURCE – Kyowa Hakko.

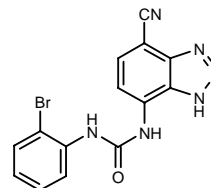
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1. Ohta, S. et al. *Inhibition of P-selectin specific cell adhesion by a low molecular weight, non-carbohydrate compound, KF38789*. Inflamm Res 2001, 50(11): 544.
2. Ohta, S. et al. *Temperature dependent inhibition of P-selectin specific cell adhesion by small molecule KF38789*. Proc Jpn Soc Immunol 2000, 30: Abst 2-F-284-P.

SB-265610

306251

N-(2-Bromophenyl)-*N'*-(4-cyano-1*H*-1,2,3-benzotriazol-7-yl)urea



C14 H9 Br N6 O; Mol wt: 357.1701

ACTION – Orally active and selective CXCR2 antagonist (IC₅₀ = 39 nM for inhibition of IL-8 binding to human CXCR2 receptors) proven to inhibit calcium mobilization and chemotaxis induced by rat cytokine-induced neutrophil chemoattractant-1 (CINC-1) in rat neutrophils (IC₅₀ = 3.7 and 70 nM, respectively). Moreover, it inhibited human and rabbit neutrophil chemotaxis induced by both IL-8 and GROα and it attenuated the antiapoptotic effect of CINC-1 in cultured peripheral neutrophils. In hyperoxia-exposed newborn rats, compound at doses of 1-3 mg/kg i.p. reduced neutrophil accumulation in bronchoalveolar lavage (> 95% decrease on day 8 at the highest dose) and lung myeloperoxidase accumulation. In a rabbit immune complex model of colitis, a dose of 25 mg/kg p.o. b.i.d. was found to decrease acute and chronic inflammation and to preserve mucosal integrity. Potentially useful for the treatment of neutrophil-mediated damage in the lung, as well as rheumatoid arthritis and inflammatory bowel disease.

SOURCE – GlaxoSmithKline.

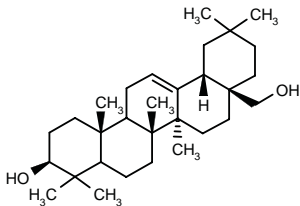
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2. Widdowson, K.L. and Rutledge, M.C. (SmithKline Beecham Corp.) *IL-8 receptor antagonists*. EP 0991406, JP 2001511130, US 6300325, WO 9832439.
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4. White, J.R. et al. *SB-265610, an IL-8 antagonist, is a potent inhibitor of PMN chemotaxis and is effective in the rabbit immune complex model of colitis*. Dig Dis Week (May 20-23, Atlanta) 2001, Abst 1439.
5. White, J.R. et al. *SB-265610, an IL-8 antagonist, is a potent inhibitor of PMN chemotaxis and is effective in the rabbit immune complex model of colitis*. Inflamm Res 2001, 50(Suppl. 3): Abst W06/04.

TREATMENT OF LIVER AND BILIARY TRACT DISORDERS

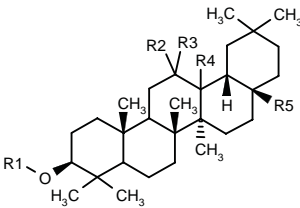
310864

Olean-12-ene-3β,28-diol



C30 H50 O2; Mol wt: 442.7230

ACTION – Agent for the treatment of hepatic diseases proven to exert a protective effect against concanavalin A-induced hepatitis when administered orally to mice (10 mg/kg, 3 doses/day). Other exemplified triterpene derivatives are:



Compound	R1	R2	R3	R4	R5	Formula
310868	H	H	bond		CH2OCH2Ph	C ₃₇ H ₅₆ O ₂
310869	H	H	bond		CO2Me	C ₃₁ H ₅₀ O ₃
310870	H	H	bond		CH=CHCO2H	C ₃₂ H ₅₀ O ₃
310875	H	H	bond		CONHBu	C ₃₄ H ₅₇ NO ₂
310877	Ac	H	bond		CO2H	C ₃₂ H ₅₀ O ₄
310880	Me	H	bond		CO2H	C ₃₁ H ₅₀ O ₃
310882	H	-O-		H	CO2H	C ₃₀ H ₄₈ O ₄

SOURCE – Meiji Seika.

REFERENCES

1. Sasaki, K. et al. (Meiji Seika Kaisha, Ltd.) *Triterpene derivs. and therapeutic agents for hepatopathy*. JP 2001240573.

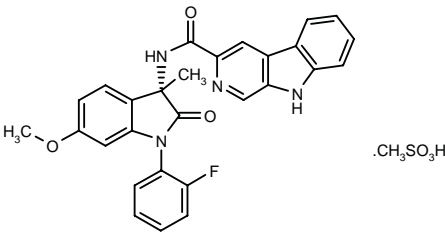
TREATMENT OF PANCREATIC DISORDERS

T-1172

311245

N-[1-(2-Fluorophenyl)-6-methoxy-3(*S*)-methyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl]-9*H*-β-carboline-3-carboxamide methanesulfonate

N-[1-(2-Fluorophenyl)-6-methoxy-3(*S*)-methyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl]-9*H*-pyrido[3,4-*b*]indole-3-carboxamide methanesulfonate



C28 H21 F N4 O3 . C H4 O3 S; Mol wt: 576.6025

ACTION – Potent and selective cholecystokinin CCK_A (CCK₁) receptor antagonist (K_i = 0.93 and 420 nM against CCK_A and CCK_B receptors, respectively), able to protect mice from cerulein-induced pancreatitis (ED₅₀ = 0.20 mg/kg) and, at higher doses, to inhibit CCK-8-induced gallbladder emptying in mice (ID₅₀ = 1.8 mg/kg). Compared to lorglumide, compound was 7- and 18-fold more selective for CCK_A receptors *in vitro* and *in vivo*, respectively. Potentially useful for the treatment of pancreatitis.

SOURCE – Tanabe Seiyaku.

REFERENCES

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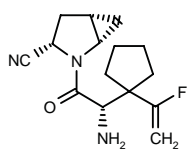
2. Kashiwagi, T. et al. *Studies on a novel, potent, and pancreas selective over gallbladder cholecystokinin - A receptor antagonist (1)*. 21st Symp Med Chem (Nov 28-30, Kyoto) 2001, Abst 2P-33.

ENDOCRINE DRUGS

ANTIDIABETIC DRUGS

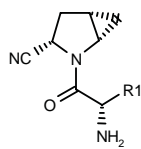
310372

(1*S*,3*S*,5*S*)-2-[2(*S*)-Amino-2-[1-(1-fluorovinyl)cyclopentyl]-acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile



C15 H20 F N3 O; Mol wt: 277.3410

ACTION – An inhibitor of dipeptidyl-peptidase IV (DPP-IV) with potential in the treatment of type 2 diabetes, obesity and disorders related therewith. Other specifically claimed cyclopropyl-fused pyrrolidine derivatives are:



Compound	R1	Formula
310373	1-(CH2OH)-cyclobutyl	C ₁₃ H ₁₉ N ₃ O ₂
310375	1-(CH2OH)-cyclohexyl	C ₁₅ H ₂₃ N ₃ O ₂
310376	1-adamantyl	C ₁₈ H ₂₅ N ₃ O
310377	3-F-1-adamantyl	C ₁₈ H ₂₄ FN ₃ O
310378	bicyclo[2.2.1]hept-1-yl	C ₁₅ H ₂₁ N ₃ O
310379	3-OH-1-adamantyl	C ₁₈ H ₂₅ N ₃ O ₂
310380	1-(CH2OH)-1-cyclopentyl	C ₁₄ H ₂₁ N ₃ O ₂

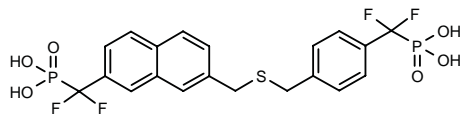
SOURCE – Bristol-Myers Squibb.

REFERENCES

1. Robl, J.A. et al. (Bristol-Myers Squibb Co.) *Cyclopropyl-fused pyrrolidine-based inhibitors of dipeptidyl peptidase IV and method.* WO 0168603.

310954

1-[7-[4-(1,1-Difluoro-1-phosphonomethyl)benzylsulfanyl-methyl]naphthalen-2-yl]-1,1-difluoromethylphosphonic acid



C20 H18 F4 O6 P2 S; Mol wt: 524.3622

ACTION – Protein-tyrosine-phosphatase PTP1B inhibitor, expected to be useful for the treatment of diabetes and obesity, as well as other PTP1B-mediated conditions including hyperlipidemia and hypercholesterolemia, atherosclerosis, vascular restenosis, inflammatory bowel disease, pancreatitis, adipose cell tumors and neurodegenerative diseases.

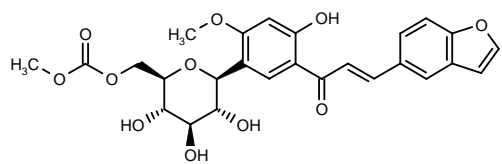
SOURCES – Banyu; Merck Frosst.

REFERENCES

1. Bayly, C. and Ohkubo, M. (Merck Frosst Canada Inc.;Banyu Pharmaceutical Co., Ltd.) *Sulfur substd. aryldifluoromethylphosphonic acids as PTP-1B inhibitors.* WO 0170753, WO 0170754.

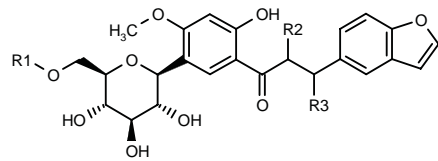
311530

1-[5-[3-(1-Benzofuran-5-yl)-2-propenoyl]-4-hydroxy-2-methoxyphenyl]-1-deoxy-β-D-glucopyranos-6-yl methyl carbonate



C26 H26 O11; Mol wt: 514.4804

ACTION – Antidiabetic agent with the ability to lower blood glucose levels, as demonstrated in SD rats. Other exemplified C-glycosides include the following:



Compound	R1	R2	R3	Formula
311532	H	bond		C ₂₄ H ₂₄ O ₉
311533	CO2Me	H	H	C ₂₆ H ₂₈ O ₁₁
311535	H	H	H	C ₂₄ H ₂₆ O ₉

SOURCE – Kotobuki.

REFERENCES

1. Toyama, Y. et al. (Kotobuki Pharmaceutical Co., Ltd.) *C-Glycosides, their preparation method and agents containing them.* JP 2001288178.

DiaPep277

296617

L-Valyl-L-leucyl-glycyl-glycyl-glycyl-L-valyl-L-alanyl-L-leucyl-L-leucyl-L-arginyl-L-valyl-L-isoleucyl-L-prolyl-L-alanyl-L-leucyl-L-aspartyl-L-seryl-L-leucyl-L-threonyl-L-prolyl-L-alanyl-L-asparaginyL-L-glutamyl-L-aspartic acid

C106 H180 N28 O34; Mol wt: 2390.7500

ACTION – Heat shock protein (hsp) peptide proven to arrest β-cell destruction and to maintain insulin production in diabetic mice, as well as to delay allograft rejection in a mouse skin transplant model. Results of a double-blind, randomized phase II study in type 1 diabetic patients showed that compound at a dose of 1 mg/kg s.c. preserves the production of C-peptide and endogenous insulin and appears to activate antiinflammatory Th2 cytokines rather than proinflammatory Th1 cytokines. Potentially useful for the treatment of type 1 diabetes.

SOURCES – Peptor; Weizmann Institute of Science, Rehovot (IL).

REFERENCES

1. Cohen, I.R. and Birk, O. (Yeda Research & Development Co. Ltd.) *Method of reducing the severity of host vs. graft reaction by down-regulating HSP60*. WO 9808536.

2. Cohen, I.R. et al. (Yeda Research & Development Co. Ltd.) *Novel peptides derived from human heat shock protein 60 for treatment of diabetes, compsns., methods and kits*. WO 9701959.

3. Cohen, I.R. et al. (Yeda Research & Development Co. Ltd.) *Peptide p277 analogs, and pharmaceutical compsns. comprising them for treatment or diagnosis of diabetes*. EP 0820303, JP 1998511649, US 6180103, WO 9619236.

4. Cohen, I.R. et al. (Yeda Research & Development Co. Ltd.) *Preparations and methods for the treatment of T cell mediated diseases*. WO 9702016.

5. Birk, O.S. et al. *The 60-kDa heat shock protein modulates allograft rejection*. Proc Natl Acad Sci USA 1999, 96(9): 5159.

6. Raz, I. et al. *β-Cell function in new-onset type 1 diabetes and immunomodulation with a heat-shock protein peptide (DiaPep277): A randomised, double-blind, phase II trial*. Lancet 2001, 358(9295): 1749.

7. Shpigel, E. et al. *Production and purification of a recombinant human hsp60 epitope using the cellulose-binding domain in Escherichia coli*. Protein Expr Purif 1998, 14(2): 185.

8. *Company Profile: Peptor*. DailyDrugNews.com (Daily Essentials) 2000, Nov 17.

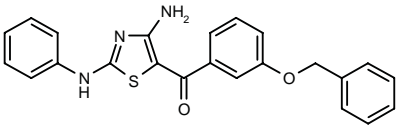
9. *First clinical data on peptide for autoimmune diabetes presented during EASD meeting*. DailyDrugNews.com (Daily Essentials) 2001, Sept 14.

10. *Peptor to begin phase II trial of DiaPep277 in treatment of LADA*. DailyDrugNews.com (Daily Essentials) 2002, Jan 15.

NNC-57-0558

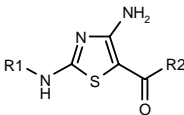
311420

1-[4-Amino-2-(phenylamino)thiazol-5-yl]-1-[3-(benzyloxy)-phenyl]methanone



C23 H19 N3 O2 S; Mol wt: 401.4881

ACTION – Potent glycogen synthase kinase-3 (GSK-3) inhibitor (IC₅₀ = 0.39 μM) with high selectivity relative to a panel of serine/threonine and tyrosine kinases, and cellular activity at 10 μM in isolated rat soleus muscle and CHO cells. *In vivo*, compound at a dose of 10 mg/kg exhibited significant glucose-lowering effects in GK rats. Potentially useful for the treatment of type 2 diabetes. Other 2,4-diaminothiazoles are:



Compound	R1	R2	Formula
NNC-57-0541* [308324]	Ph	cyclopropyl	C ₁₃ H ₁₃ N ₃ OS
NNC-57-0588** [308326]	Pr	3-Pyr	C ₁₂ H ₁₄ N ₄ OS
NNC-57-0545 [311418]	Ph	3-Pyr	C ₁₅ H ₁₂ N ₄ OS
NNC-57-0734 [311421]	4-Cl-Ph	3-(PhCH2O)-Ph	C ₂₃ H ₁₈ ClN ₃ O ₂ S

SOURCE – Novo Nordisk.

REFERENCES

1. Bowler, A.N. et al. (Novo Nordisk A/S) *2,4-Diaminothiazole derivs*. WO 0156567.

2. Bowler, A.N. et al. *2,4-Diaminothiazoles: A novel class of glycogen synthase kinase-3 (GSK-3) inhibitors*. 11th RSC-SCI Med Chem Symp (Sept 9-12, Cambridge) 2001, Abst P20.

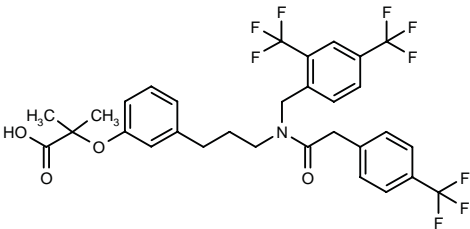
*Identified compound **308324** Drug Data Rep 2001, 023(10): 0991.

Identified compound **308326 (see **308324**) Drug Data Rep 2001, 023(10): 0991.

TREATMENT OF DIABETIC COMPLICATIONS

311494

2-[3-[3-[N-[2,4-Bis(trifluoromethyl)benzyl]-2-[4-(trifluoromethyl)phenyl]acetamido]propyl]phenoxy]-2-methylpropionic acid



C31 H28 F9 N O4; Mol wt: 649.5472

ACTION – Dual agonist of the peroxisome proliferator-activated receptors PPAR γ and PPAR δ , with more than 30-fold selectivity relative to PPAR α (EC_{50} = 4, 19 and 620 nM, respectively, in functional assays for human PPAR; EC_{50} = 28, 19 and > 1000 nM, respectively, in murine PPAR). Following oral administration to ZDF rats at a dose of 30 mg/kg b.i.d., compound reduced plasma glucose and serum triglyceride levels by 47 and 51%, respectively, and increased HDL cholesterol levels by 24%. Potentially useful for the treatment of the metabolic syndrome X.

SOURCE – GlaxoSmithKline.

REFERENCES

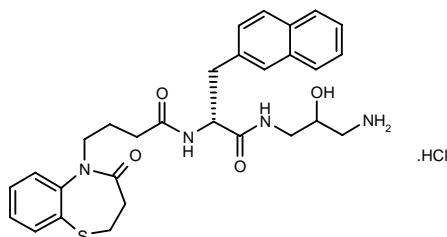
1. Liu, K.G. et al. *Identification of a series of PPARgamma/delta dual agonists via solid-phase parallel synthesis*. *Bioorg Med Chem Lett* 2001, 11(22): 2959.

TREATMENT OF GROWTH HORMONE SECRETION DISORDERS

S-37435

311363

N-[1(*R*)-[*N*-(3-Amino-2-hydroxypropyl)carbamoyl]-2-naphthylethyl]-4-(4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-5-yl)butyramide hydrochloride



C29 H34 N4 O4 S . HCl; Mol wt: 571.1385

ACTION – Potent nonpeptide growth hormone secretagogue incorporating a benzodiazepine scaffold with nanomolar activity (EC_{50} = 1 nM) in the rat pituitary cell assay. Potentially useful for growth hormone replacement therapy.

SOURCES – Kaken; Molecular Research Institute, Mountain View, CA (US).

REFERENCES

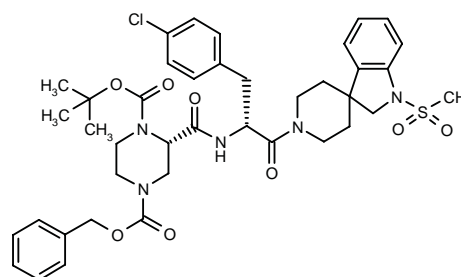
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2. Huang, P. et al. *Rational design, discovery, and synthesis of a novel series of potent growth hormone secretagogues*. *J Med Chem* 2001, 44(24): 4082.

TREATMENT OF MALE SEXUAL DYSFUNCTION

310757

2(*S*)-[*N*-[1(*R*)-(4-Chlorobenzyl)-2-[1-(methylsulfonyl)-spiro[2,3-dihydro-1*H*-indole-3,4'-piperidin]-1'-yl]-2-oxoethyl]carbamoyl]piperazine-1,4-dicarboxylic acid 4-benzyl 1-*tert*-butyl diester



C40 H48 Cl N5 O8 S; Mol wt: 794.3652

ACTION – A representative compound from a series of spiropiperidines with selective agonist activity at the melanocortin MC₄ receptor. Potentially useful for the treatment of obesity, diabetes and female or male sexual disorders including erectile dysfunction.

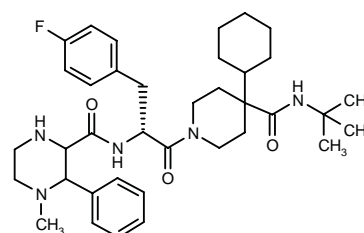
SOURCE – Merck & Co.

REFERENCES

1. Palucki, B.L. and Nargund, R.P. (Merck & Co., Inc.) *Spiropiperidine derivs. as melanocortin receptor agonists*. WO 0170337.

310761

N-[2-[4-(*N*-*tert*-Butylcarbamoyl)-4-cyclohexylpiperidin-1-yl]-1(*R*)-(4-fluorobenzyl)-2-oxoethyl]-4-methyl-3-phenylpiperazine-2-carboxamide



C37 H52 F N5 O3; Mol wt: 633.8478

ACTION – A representative compound from a series of substituted piperidines with selective agonist activity at the melanocortin MC₄ receptor. Potentially useful for the treatment of obesity, diabetes and female or male sexual disorders including erectile dysfunction.

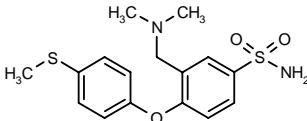
SOURCE – Merck & Co.

REFERENCES

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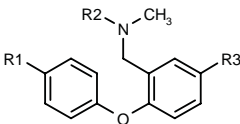
311170

3-(Dimethylaminomethyl)-4-[4-(methylsulfanyl)phenoxy]-benzenesulfonamide



C16 H20 N2 O3 S2; Mol wt: 352.4770

ACTION – Agent with the ability to inhibit monoamine reuptake, particularly 5-HT reuptake, expected to be useful for the treatment of premature ejaculation, as well as other 5-HT-mediated conditions such as depression, attention deficit hyperactivity disorder, obsessive–compulsive disorder, posttraumatic stress disorder and substance abuse. Other specifically claimed diphenyl ether compounds include the following:



Compound	R1	R2	R3	Formula
311172	OCF3	Me	SO2NH2	C ₁₆ H ₁₇ F ₃ N ₂ O ₄ S
311173	SMe	Me	(S)-SO2NHCH(Me)CH2OH	C ₁₉ H ₂₆ N ₂ O ₄ S ₂
311175	SMe	Me	CN	C ₁₇ H ₁₈ N ₂ OS
311176	OCF3	Me	CONH2	C ₁₇ H ₁₇ F ₃ N ₂ O ₃
311177	CF3	Me	NHSO2Me	C ₁₇ H ₁₉ F ₃ N ₂ O ₃ S
311178	SMe	H	CONHMe	C ₁₇ H ₂₀ N ₂ O ₂ S
311181	SMe	H	1,2,3-triazol-1-yl	C ₁₇ H ₁₈ N ₄ OS
311182	SMe	Me	1,2,4-triazol-1-yl	C ₁₈ H ₂₀ N ₄ OS
311185	SMe	H	3-NH2-1-pyrazolyl	C ₁₈ H ₂₀ N ₄ OS

SOURCE – Pfizer.

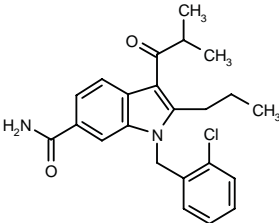
REFERENCES

1. Andrews, M.D. et al. (Pfizer Ltd.;Pfizer Inc.) *Diphenyl ether cpds. useful in therapy.* WO 0172687.

FR-181074*

243743

1-(2-Chlorobenzyl)-3-isobutyryl-2-propylindole-6-carboxamide



C23 H25 Cl N2 O2; Mol wt: 396.9210

ACTION – Phosphodiesterase type 5 (PDE5) inhibitor (IC₅₀ = 0.3 nM against human platelet enzyme) potentially useful for the treatment of erectile dysfunction.

SOURCE – Fujisawa.

REFERENCES

1. Nomoto, A. et al. (Fujisawa Pharmaceutical Co., Ltd.) *Novel use.* JP 1998067682.

2. Oku, T. et al. (Fujisawa Pharmaceutical Co., Ltd.) *Indole derivs. as cGMP-PDE inhibitors.* EP 0820441, JP 1999503445, WO 9632379.

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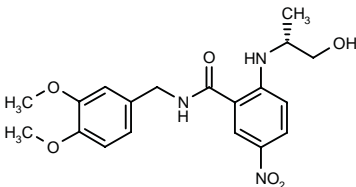
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*Identified compound **243743** Drug Data Rep 1997, 019(02): 0141.

FR-226807*

282381

N-(3,4-Dimethoxybenzyl)-2-[2-hydroxy-1 (R)-methylethyl-amino]-5-nitrobenzamide



C19 H23 N3 O6; Mol wt: 389.4057

ACTION – Potent and selective phosphodiesterase type 5 (PDE5) inhibitor (IC₅₀ = 1.1 nM) with 18-fold selectivity over PDE6 and > 1,000-fold selectivity over PDE1, PDE2, PDE3 and PDE4. In isolated rabbit corpus cavernosus, compound increased cGMP levels, induced muscle relaxation and enhanced relaxation evoked by electrical field stimulation. Moreover, it attenuated the responsiveness of the corpus cavernosus in middle-aged and streptozotocin-diabetic rats. In anesthetized dogs, compound (0.032-0.1 mg/kg i.v.) was shown to prolong the time to return to 75% of maximal intracavernosal pressure following electrical stimulation of the pelvic nerve, being more potent than sildenafil. Compound exhibited a superior safety profile compared to sildenafil, with less hypotensive effect in anesthetized dogs. Potentially useful for the treatment of erectile dysfunction.

SOURCE – Fujisawa.

REFERENCES

1. Oku, T. et al. (Fujisawa Pharmaceutical Co., Ltd.) *Anthranilic acid derivs. as inhibitors of the cGMP-phosphodiesterase.* EP 1080069, JP 2001508811, WO 9954284.

2. Hosogai, N. et al. *Effect of FR226807, a selective phosphodiesterase 5 inhibitor, on the attenuated responsiveness of the corpus cavernosum in middle-aged and streptozotocin-induced diabetic rats.* Jpn J Pharmacol 2001, 85(Suppl. I): Abst P-894.

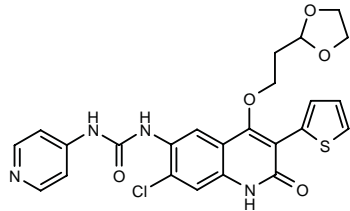
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*Identified compound **282381** (see **282379**) Drug Data Rep 1999, 021(11): 0984.

TREATMENT OF GYNECOLOGICAL DISORDERS

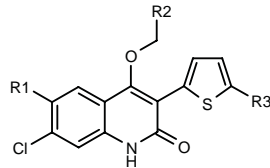
310723

N-[7-Chloro-4-[2-(1,3-dioxolan-2-yl)ethoxy]-2-oxo-3-(2-thienyl)-1,2-dihydroquinolin-6-yl]-*N'*-(4-pyridyl)urea



C24 H21 Cl N4 O5 S; Mol wt: 512.9719

ACTION – Gonadotropin-releasing hormone antagonist, expected to be useful for the treatment of a variety of male and female sex hormone-related disorders including hormone-dependent cancers, endometriosis, polycystic ovarian disease, precocious puberty and premenstrual syndrome, among others. Other specifically claimed compounds are:



Compound	R1	R2	R3	Formula
310724	4-Pyr-NHCONH	cyclopentyl-CH2	H	C ₂₆ H ₂₅ ClN ₄ O ₃ S
310725	4-Pyr-NHCONH	2-oxetanyl	H	C ₂₃ H ₁₉ ClN ₄ O ₄ S
310726	4-Pyr-NHCONH	tetrahydro-2-thienyl-CH2	H	C ₂₅ H ₂₃ ClN ₄ O ₃ S ₂
310727	4-Pyr-NHCONH	1-oxo-tetrahydro-2-thienyl	H	C ₂₅ H ₂₃ ClN ₄ O ₄ S ₂
310728	4-Pyr-NHCONH	1,1-dioxo-tetrahydro-2-thienyl-CH2	H	C ₂₅ H ₂₃ ClN ₄ O ₅ S ₂
310729	4-Pyr-NHCONH	2-THF-CH2	H	C ₂₅ H ₂₃ ClN ₄ O ₄ S
310731	4-pyrimidinyl-NHCO	1,3-dioxolan-2-yl-CH2	Cl	C ₂₃ H ₁₈ Cl ₂ N ₄ O ₃ S
310732	4-pyrimidinyl-NHCO	cyclopentyl-CH2	Cl	C ₂₅ H ₂₂ Cl ₂ N ₄ O ₃ S
310733	4-pyrimidinyl-NHCO	2-oxetanyl	Cl	C ₂₂ H ₁₆ Cl ₂ N ₄ O ₄ S
310734	4-pyrimidinyl-NHCO	tetrahydro-2-thienyl-CH2	Cl	C ₂₄ H ₂₀ Cl ₂ N ₄ O ₃ S ₂
310735	4-pyrimidinyl-NHCO	1-oxo-tetrahydro-2-thienyl	Cl	C ₂₄ H ₂₀ Cl ₂ N ₄ O ₄ S ₂
310736	4-pyrimidinyl-NHCO	1,1-dioxo-tetrahydro-2-thienyl-CH2	Cl	C ₂₄ H ₂₀ Cl ₂ N ₄ O ₅ S ₂
310737	4-pyrimidinyl-NHCO	2(S)-oxetanyl-CH2	Cl	C ₂₃ H ₁₈ Cl ₂ N ₄ O ₄ S
310738	4-pyrimidinyl-NHCO	2-THF-CH2	Cl	C ₂₄ H ₂₀ Cl ₂ N ₄ O ₄ S

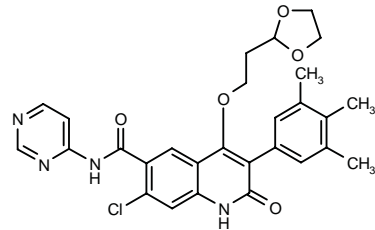
SOURCE – Merck & Co.

REFERENCES

1. Devita, R.J. et al. (Merck & Co., Inc.) *Antagonists of gonadotropin releasing hormone*. WO 0170227.

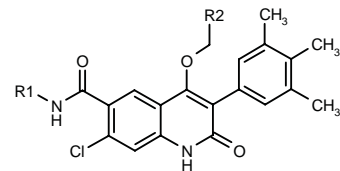
310739

7-Chloro-4-[2-(1,3-dioxolan-2-yl)ethoxy]-2-oxo-*N*-(4-pyrimidinyl)-3-(3,4,5-trimethylphenyl)-1,2-dihydroquinoline-6-carboxamide



C28 H27 Cl N4 O5; Mol wt: 534.9973

ACTION – Gonadotropin-releasing hormone antagonist, expected to be useful for the treatment of a variety of male and female sex hormone-related disorders including hormone-dependent cancers, endometriosis, polycystic ovarian disease, precocious puberty and premenstrual syndrome, among others. Other specifically claimed compounds are:



Compound	R1	R2	Formula
310740	4-pyrimidinyl	cyclopentyl-CH2	C ₃₀ H ₃₁ ClN ₄ O ₃
310742	4-pyrimidinyl	2-oxetanyl	C ₂₇ H ₂₅ ClN ₄ O ₄
310743	4-pyrimidinyl	tetrahydro-2-thienyl-CH2	C ₂₉ H ₂₉ ClN ₄ O ₃ S
310744	4-pyrimidinyl	1-oxo-tetrahydro-2-thienyl	C ₂₉ H ₂₉ ClN ₄ O ₄ S
310745	4-pyrimidinyl	1,1-dioxo-tetrahydro-2-thienyl-CH2	C ₂₉ H ₂₉ ClN ₄ O ₅ S
310746	4-pyrimidinyl	2-THF-CH2	C ₂₉ H ₂₉ ClN ₄ O ₄
310748	1,2,5-thiadiazol-3-yl	1,3-dioxolan-2-yl-CH2	C ₂₆ H ₂₅ ClN ₄ O ₃ S
310749	1,2,5-thiadiazol-3-yl	cyclopentyl-CH2	C ₂₈ H ₂₉ ClN ₄ O ₃ S
310750	1,2,5-thiadiazol-3-yl	2-oxetanyl	C ₂₅ H ₂₃ ClN ₄ O ₄ S
310751	1,2,5-thiadiazol-3-yl	tetrahydro-2-thienyl-CH2	C ₂₇ H ₂₇ ClN ₄ O ₃ S ₂
310752	1,2,5-thiadiazol-3-yl	1-oxo-tetrahydro-2-thienyl	C ₂₇ H ₂₇ ClN ₄ O ₄ S ₂
310753	1,2,5-thiadiazol-3-yl	1,1-dioxo-tetrahydro-2-thienyl-CH2	C ₂₇ H ₂₇ ClN ₄ O ₅ S ₂
310754	1,2,5-thiadiazol-3-yl	2(S)-oxetanyl-CH2	C ₂₆ H ₂₅ ClN ₄ O ₄ S

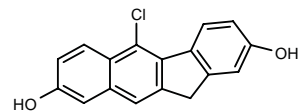
SOURCE – Merck & Co.

REFERENCES

1. Devita, R.J. et al. (Merck & Co., Inc.) *Antagonists of gonadotropin releasing hormone*. WO 0170228.

311209

5-Chloro-11*H*-benzo[*b*]fluorene-2,8-diol



C17 H11 Cl O2; Mol wt: 282.7249

ACTION – A representative compound from a series of nonsteroidal tetracyclic compounds effective as estrogen receptor (ER) modulators. Compound demonstrated affinity for human ERβ receptors expressed in CHO cells, being > 30-fold selective over ERα receptors. Potentially useful as a contraceptive and in the treatment of benign prostatic hypertrophy, cardiovascular disorders, menopausal complaints, osteoporosis, estrogen-dependent tumors and CNS disorders such as depression and Alzheimer’s disease.

SOURCE – Akzo Nobel.

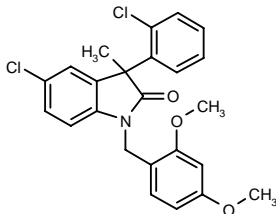
REFERENCES

1. Veeneman, G. et al. (Akzo Nobel N.V.) *Non-steroidal, tetracyclic cpds. for estrogen-related treatments.* WO 0172713.

**UTERINE STIMULANTS AND
Tocolytics**

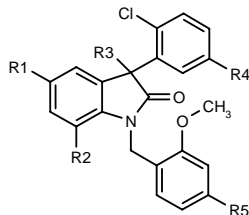
311677

5-Chloro-3-(2-chlorophenyl)-1-(2,4-dimethoxybenzyl)-3-methyl-2,3-dihydro-1*H*-indol-2-one



C24 H21 Cl2 N O3; Mol wt: 442.3399

ACTION – Oxytocin receptor antagonist, as demonstrated *in vitro* by an IC₅₀ of 3.2 nM, potentially useful as a tocolytic or uterine relaxant. Other exemplified indolin-2-one derivatives include the following:



Compound	R1	R2	R3	R4	R5	Formula
311679	Cl	H	OH	H	OMe	C ₂₃ H ₁₉ Cl ₂ NO ₄
311680	Cl	H	Me	H	N(Et)2	C ₂₇ H ₂₈ Cl ₂ N ₂ O ₂
311681	Cl	H	Me	3-Pyr-CON(Me)	OMe	C ₃₁ H ₂₇ Cl ₂ N ₃ O ₄
311682	Cl	H	Me	2(S)-(MeOCH2)-1-pyrrolidinyl-CO	OMe	C ₃₁ H ₃₂ Cl ₂ N ₂ O ₅
311683	Cl	H	Me	CH2N(Me)Ac	OMe	C ₂₈ H ₂₈ Cl ₂ N ₂ O ₄
311685	Cl	H	Me	CON(Et)CH2CF3	OMe	C ₂₉ H ₂₇ Cl ₂ F ₃ N ₂ O ₄
311686	Cl	Cl	Me	NH2	OMe	C ₂₄ H ₂₁ Cl ₃ N ₂ O ₃
311687	H	H	Me	CON(Et)2	OMe	C ₂₈ H ₃₁ ClN ₂ O ₄

SOURCE – Sanofi-Synthélabo.

REFERENCES

1. Foulon, L. et al. (Sanofi-Synthélabo) *Indolin-2-one derivs., preparation and their use as ocytonin receptor ligands.* FR 2807038, WO 0174775.

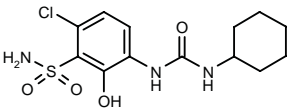
DERMATOLOGIC DRUGS

ANTIPSORIATICS

310457

6-Chloro-3-(3-cyclohexylureido)-2-hydroxybenzene-sulfonamide

N-(4-Chloro-2-hydroxy-3-sulfamoylphenyl)-*N'*-cyclohexyl-urea



C13 H18 Cl N3 O4 S; Mol wt: 347.8212

ACTION – IL-8 (CXCR1, CXCR2) receptor antagonist with potential in the treatment of chemokine-mediated conditions including psoriasis, atopic dermatitis, arthritis, asthma, chronic obstructive pulmonary disease (COPD), adult respiratory distress syndrome (ARDS), inflammatory bowel disease, Crohn’s disease, ulcerative colitis, stroke, septic shock, multiple sclerosis, cardiac and renal reperfusion injury, glomerulonephritis, thrombosis, Alzheimer’s disease, transplant rejection, malaria, restenosis, angiogenesis, atherosclerosis, osteoporosis, etc.

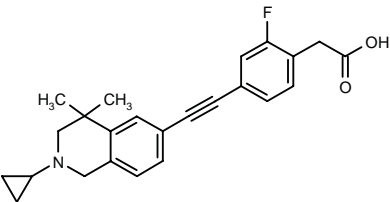
SOURCE – GlaxoSmithKline.

REFERENCES

1. Widdowson, K.L. and Jin, Q. (SmithKline Beecham Corp.) *IL-8 receptor antagonists.* WO 0168084.

310937

2-[4-[2-(2-Cyclopropyl-4,4-dimethyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)ethynyl]-2-fluorophenyl]acetic acid



C24 H24 F N O2; Mol wt: 377.4566

ACTION – A representative compound from a series of nonsteroidal tetracyclic compounds effective as estrogen receptor (ER) modulators. Compound demonstrated affinity for human ERβ receptors expressed in CHO cells, being > 30-fold selective over ERα receptors. Potentially useful as a contraceptive and in the treatment of benign prostatic hypertrophy, cardiovascular disorders, menopausal complaints, osteoporosis, estrogen-dependent tumors and CNS disorders such as depression and Alzheimer’s disease.

SOURCE – Akzo Nobel.

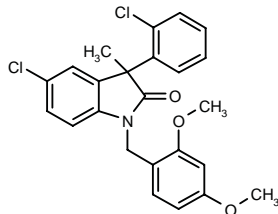
REFERENCES

1. Veeneman, G. et al. (Akzo Nobel N.V.) *Non-steroidal, tetracyclic cpds. for estrogen-related treatments.* WO 0172713.

UTERINE STIMULANTS AND TOCOLYTICS

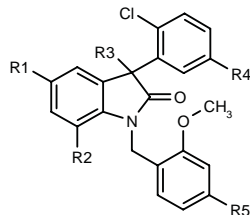
311677

5-Chloro-3-(2-chlorophenyl)-1-(2,4-dimethoxybenzyl)-3-methyl-2,3-dihydro-1*H*-indol-2-one



C24 H21 Cl2 N O3; Mol wt: 442.3399

ACTION – Oxytocin receptor antagonist, as demonstrated *in vitro* by an IC₅₀ of 3.2 nM, potentially useful as a tocolytic or uterine relaxant. Other exemplified indolin-2-one derivatives include the following:



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311681	Cl	H	Me	3-Pyr-CON(Me)	OMe	C ₃₁ H ₂₇ Cl ₂ N ₃ O ₄
311682	Cl	H	Me	2(S)-(MeOCH2)-1-pyrrolidinyl-CO	OMe	C ₃₁ H ₃₂ Cl ₂ N ₂ O ₅
311683	Cl	H	Me	CH2N(Me)Ac	OMe	C ₂₈ H ₂₈ Cl ₂ N ₂ O ₄
311685	Cl	H	Me	CON(Et)CH2CF3	OMe	C ₂₉ H ₂₇ Cl ₂ F ₃ N ₂ O ₄
311686	Cl	Cl	Me	NH2	OMe	C ₂₄ H ₂₁ Cl ₃ N ₂ O ₃
311687	H	H	Me	CON(Et)2	OMe	C ₂₈ H ₃₁ ClN ₂ O ₄

SOURCE – Sanofi-Synthélabo.

REFERENCES

1. Foulon, L. et al. (Sanofi-Synthélabo) *Indolin-2-one derivs., preparation and their use as ocytonin receptor ligands.* FR 2807038, WO 0174775.

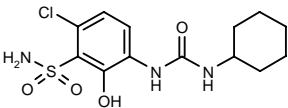
DERMATOLOGIC DRUGS

ANTIPSORIATICS

310457

6-Chloro-3-(3-cyclohexylureido)-2-hydroxybenzene-sulfonamide

N-(4-Chloro-2-hydroxy-3-sulfamoylphenyl)-*N'*-cyclohexyl-urea



C13 H18 Cl N3 O4 S; Mol wt: 347.8212

ACTION – IL-8 (CXCR1, CXCR2) receptor antagonist with potential in the treatment of chemokine-mediated conditions including psoriasis, atopic dermatitis, arthritis, asthma, chronic obstructive pulmonary disease (COPD), adult respiratory distress syndrome (ARDS), inflammatory bowel disease, Crohn’s disease, ulcerative colitis, stroke, septic shock, multiple sclerosis, cardiac and renal reperfusion injury, glomerulonephritis, thrombosis, Alzheimer’s disease, transplant rejection, malaria, restenosis, angiogenesis, atherosclerosis, osteoporosis, etc.

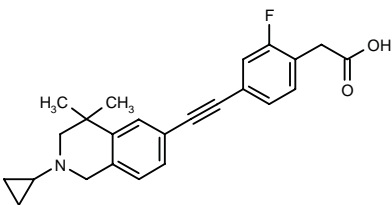
SOURCE – GlaxoSmithKline.

REFERENCES

1. Widdowson, K.L. and Jin, Q. (SmithKline Beecham Corp.) *IL-8 receptor antagonists.* WO 0168084.

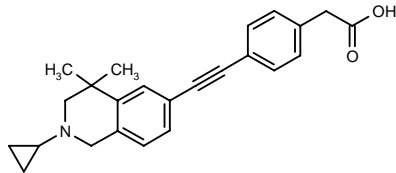
310937

2-[4-[2-(2-Cyclopropyl-4,4-dimethyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)ethynyl]-2-fluorophenyl]acetic acid



C24 H24 F N O2; Mol wt: 377.4566

ACTION – Retinoic acid-inducible cytochrome P-450 (P-450RAI) inhibitor that displayed an IC₅₀ of 1.6 μM against P-450RAI-1 expressed in HeLa cells. In the SKH1-hrBR mouse model of topical irritation, compound produced only slight effects at the highest dose tested (1000 nmol/25 g). Potentially useful for the treatment of a broad range of conditions including skin disorders such as actinic keratoses, acne, psoriasis, eczema and atopic dermatitis, as well as other diseases including type 2 diabetes, cancer, eye diseases, dyslipidemia, postangioplasty restenosis, human papillomavirus infections, pulmonary fibrosis, colitis, Alzheimer’s disease, Parkinson’s disease, stroke and pituitary dysfunction. Another exemplified cyclopropyl-substituted isoquinoline is:



310938: C24 H25 N O2

SOURCE – Allergan.

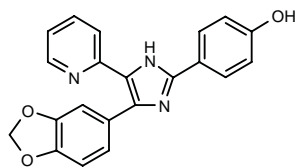
REFERENCES

1. Vasudevan, J. et al. (Allergan, Inc.) *Cpds. having activity as inhibitors of cytochrome P450RAI*. US 6303785.

WOUND-HEALING AGENTS

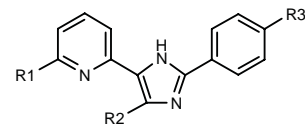
311210

4-[4-(1,3-Benzodioxol-5-yl)-5-(2-pyridyl)-1*H*-imidazol-2-yl]phenol



C21 H15 N3 O3; Mol wt: 357.3675

ACTION – Agent with the ability to interfere with the tumor growth factor-β (TGF-β) signaling pathway through inhibition of ALK5 kinase. Potentially useful for the treatment of chronic and acute renal diseases, for wound healing, arthritis, osteoporosis, congestive heart failure, ulcers, ocular disorders, diabetic nephropathy, Alzheimer’s disease, atherosclerosis, fibrosis and restenosis. Other specifically claimed triarylimidazole derivatives include the following:



Compound	R1	R2	R3	Formula
311211	H	1,3-benzodioxol-5-yl	2H-tetrazol-5-yl	C ₂₂ H ₁₅ N ₇ O ₂
311212	Me	4-F-3-MeO-Ph	CONH2	C ₂₃ H ₁₉ FN ₄ O ₂
311213	Me	3-F-4-MeO-Ph	CONH2	C ₂₃ H ₁₉ FN ₄ O ₂
311214	Me	2,1,3-benzoxadiazol-5-yl	CONH2	C ₂₂ H ₁₆ N ₆ O ₂
311215	Me	6-MeO-2-Naph	CONH2	C ₂₇ H ₂₂ N ₄ O ₂
311216	Me	2,1,3-benzothiadiazol-5-yl	CONH2	C ₂₂ H ₁₆ N ₆ OS
311217	Me	1,3-benzodioxol-5-yl	CONH2	C ₂₃ H ₁₈ N ₄ O ₃
311218	Me	6-quinoxaliny	CONH2	C ₂₄ H ₁₈ N ₆ O

SOURCE – GlaxoSmithKline.

REFERENCES

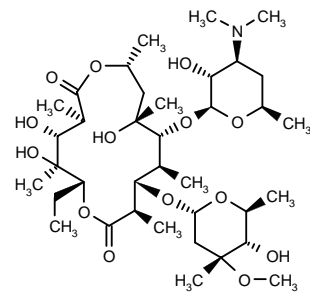
1. Harling, J.D. and Gaster, L.M. (SmithKline Beecham Corp.) *Triarylimidazole derivs. as cytokine inhibitors*. WO 0172737.

ANTIINFECTIVE THERAPY

ANTIBIOTICS

310969

8a-Homo-8a-oxaerythromycin A



C37 H67 N O14; Mol wt: 749.9293

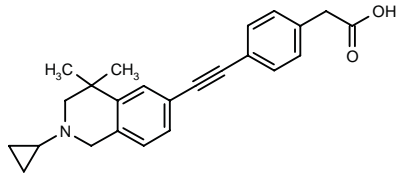
ACTION – Antibacterial 8a-oxa-8a-homoerythromycin derivative with MIC values below 1 μg/ml against the bacterial strains *Staphylococcus aureus* 209P JC-1, *Streptococcus pyogenes* O-203, *Streptococcus pneumoniae* type III and *Branhamella catarrhalis* SR11341.

SOURCE – Shionogi.

REFERENCES

1. Ikukawa, Y. et al. (Shionogi & Co. Ltd.) *8a-Oxahomoerythromycin derivs., their preparation method, intermediates for synthesis and medical compsns.* JP 2001247595.

ACTION – Retinoic acid-inducible cytochrome P-450 (P-450RAI) inhibitor that displayed an IC₅₀ of 1.6 μM against P-450RAI-1 expressed in HeLa cells. In the SKH1-hrBR mouse model of topical irritation, compound produced only slight effects at the highest dose tested (1000 nmol/25 g). Potentially useful for the treatment of a broad range of conditions including skin disorders such as actinic keratoses, acne, psoriasis, eczema and atopic dermatitis, as well as other diseases including type 2 diabetes, cancer, eye diseases, dyslipidemia, postangioplasty restenosis, human papillomavirus infections, pulmonary fibrosis, colitis, Alzheimer’s disease, Parkinson’s disease, stroke and pituitary dysfunction. Another exemplified cyclopropyl-substituted isoquinoline is:



310938: C24 H25 N O2

SOURCE – Allergan.

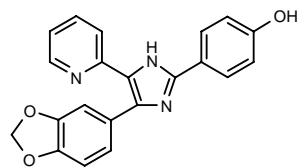
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1. Vasudevan, J. et al. (Allergan, Inc.) *Cpds. having activity as inhibitors of cytochrome P450RAI*. US 6303785.

WOUND-HEALING AGENTS

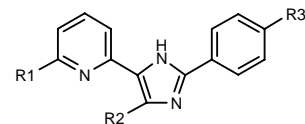
311210

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C21 H15 N3 O3; Mol wt: 357.3675

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311213	Me	3-F-4-MeO-Ph	CONH2	C ₂₃ H ₁₉ FN ₄ O ₂
311214	Me	2,1,3-benzoxadiazol-5-yl	CONH2	C ₂₂ H ₁₆ N ₆ O ₂
311215	Me	6-MeO-2-Naph	CONH2	C ₂₇ H ₂₂ N ₄ O ₂
311216	Me	2,1,3-benzothiadiazol-5-yl	CONH2	C ₂₂ H ₁₆ N ₆ OS
311217	Me	1,3-benzodioxol-5-yl	CONH2	C ₂₃ H ₁₈ N ₄ O ₃
311218	Me	6-quinoxaliny	CONH2	C ₂₄ H ₁₈ N ₆ O

SOURCE – GlaxoSmithKline.

REFERENCES

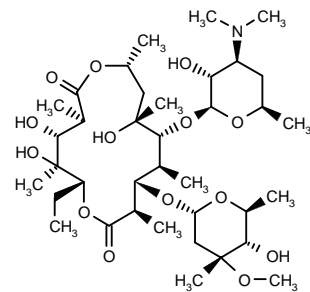
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ANTIINFECTIVE THERAPY

ANTIBIOTICS

310969

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C37 H67 N O14; Mol wt: 749.9293

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SOURCE – Shionogi.

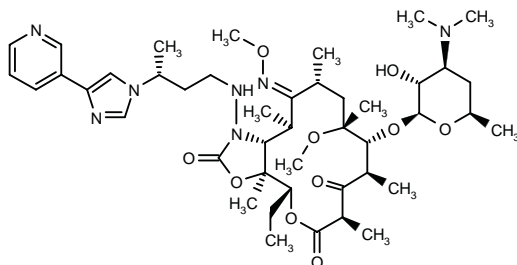
REFERENCES

1. Ikukawa, Y. et al. (Shionogi & Co. Ltd.) *8a-Oxahomoerythromycin derivs., their preparation method, intermediates for synthesis and medical compsns.* JP 2001247595.

CP-642959

313033

11-Amino-11-deoxy-3-des(hexopyranosyloxy)-9-deoxy-9-(methoxyimino)-6-*O*-methyl-3-oxo-11-[3(*R*)-[4-(3-pyridyl)imidazol-1-yl]butylhydrazino]erythromycin A 11-*N*¹,12-*O*-cyclic carbamate



C44 H69 N7 O10; Mol wt: 856.0681

ACTION – Ketolide antibiotic with antibacterial activity comparable to telithromycin against macrolide-susceptible and -resistant pneumococci (MIC₉₀ = 0.03-0.5 µg/ml) and 2-fold lower against *Haemophilus influenzae* (MIC₉₀ = 8 and 4 µg/ml, respectively). In murine models of peritonitis and pneumonia caused by *Streptococcus pneumoniae*, compound exhibited oral efficacy approximately 1-4-fold lower than that of telithromycin (ED₅₀ = 17.8-90.8 and 4.3-30.7 mg/kg p.o., respectively). In a gerbil *H. influenzae* middle ear infection model, it exhibited equivalent activity to telithromycin (ED₅₀ = 28.8 and 22 mg/kg p.o., respectively). Compound was rapidly absorbed in mice after oral administration and demonstrated dose-dependent pharmacokinetics; the AUC/MIC and C_{max}/MIC were highly correlated with *in vivo* activity.

SOURCE – Pfizer.

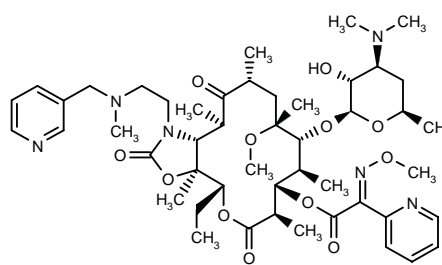
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1. Kaneko, T. et al. (Pfizer Products Inc.) *Carbamate and carbazate ketolide antibiotics*. EP 1115732, WO 0017218.
2. Kaneko, T. et al. (Pfizer Products Inc.) *Synthesis of carbamate ketolide antibiotics*. EP 1088828, JP 2001151792.
3. Girard, D. et al. *In vivo antibacterial activity of CP-642,959, a new C-9 oxime ketolide against resistant pneumococci and Haemophilus influenzae*. 41st Intersci Conf Antimicrob Agents Chemother (Dec 16-19, Chicago) 2001, Abst F-1169.
4. Girard, D. et al. *Pharmacokinetics and pharmacodynamics of CP-642,959 in murine lung infection models*. 41st Intersci Conf Antimicrob Agents Chemother (Dec 16-19, Chicago) 2001, Abst F-1170.
5. Su, W. et al. *The in vitro and in vivo activity of CP-642,959 and its related diastereomers*. 41st Intersci Conf Antimicrob Agents Chemother (Dec 16-19, Chicago) 2001, Abst F-1168.

FMA-0713*

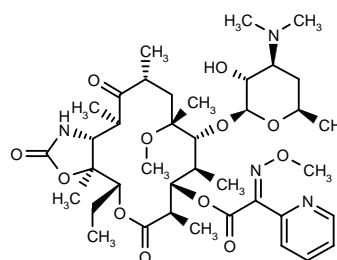
303548

11-Deoxy-3-*O*-des(hexopyranosyl)-3-*O*-[2-(methoxyimino)-2-(2-pyridyl)acetyl]-6-*O*-methyl-11-[2-[*N*-methyl-*N*-(pyridin-3-ylmethyl)amino]ethylamino]erythromycin A 11-*N*,12-*O*-cyclic carbamate



C48 H72 N6 O12; Mol wt: 925.1268

ACTION – Macrolide antibiotic (acylide) active against *Streptococcus pneumoniae* including efflux-resistant strains and macrolide-lincosamide-streptogramin B (MLS_B)-resistant strains (MIC = 0.10-0.78 µg/ml). Another related compound is:



FMA-0824 [311250]: C39 H60 N4 O12

SOURCE – Taisho.

REFERENCES

1. Asaga, T. et al. (Taisho Pharmaceutical Co., Ltd.) *Macrolides*. JP 2001072699.
2. Tanikawa, T. et al. *Synthesis and evaluation of alpha-alkoxyimino acyclides and their structure-activity relationship*. 21st Symp Med Chem (Nov 28-30, Kyoto) 2001, Abst 1P-09.

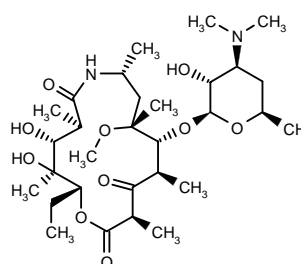
*Identified compound **303548** Drug Data Rep 2001, 023(08): 0797.

PL-1023¹⁻⁵

312701

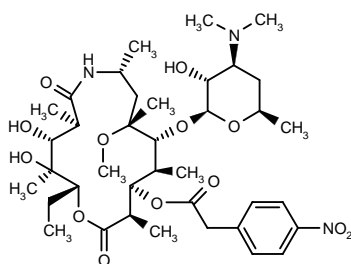
3-Des(hexopyranosyloxy)-6-*O*-methyl-3-oxo-8a-aza-8a-homoerythromycin A

GW-581506X



C30 H54 N2 O10; Mol wt: 602.7606

ACTION – Macrolide antibiotic with antimicrobial activity comparable to azithromycin against Gram-positive bacteria and activity against inducible MLS-resistant *Staphylococcus aureus* *in vitro*. Moreover, like azithromycin it was active against *Haemophilus influenzae* (MIC₉₀ = 4-8 µg/ml) and *Moraxella catarrhalis* (MIC₉₀ = 0.25 µg/ml). It exhibited a favorable pharmacokinetic profile in mice, similar to azithromycin, with very rapid absorption and sustained plasma concentrations (C_{max} = 12.45 µg/ml; t_{max} = 30 min; t_{1/2} = 5.29 h). The *in vivo* efficacy of compound in a murine model of septicemia caused by iMLS_B *S. aureus* was comparable to that of azithromycin, but it was less active than azithromycin against septicemia induced by erythromycin-susceptible *S. aureus*. Another related compound is:



PL-1441 [312702]²⁻⁵ C38 H61 N3 O13
GW-587726X

SOURCES – GlaxoSmithKline; Pliva.

REFERENCES

1. Kobrehel, G. et al. (Pliva dd) *15-Membered lactams ketolides with antibacterial activity*. EP 1070077, US 6110965, WO 9951616.
2. Lazarevski, G. et al. (Pliva dd) *Novel 8a- and 9a-15-membered lactams*. WO 0063223.
3. Alihodzic, S. et al. *Synthesis and antibacterial activity of isomeric 15-membered azalides*. 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2001, Abst 1177.
4. Lauriola, C. et al. *Interaction of novel macrolides with ery-S and ery-R ribosomes*. 6th Int Conf Macrolides Azalides Streptogramins Ketolides Oxazolidinones (Jan 23-25, Bologna) 2002, Abst 1.01.
5. Savatini, D. et al. *In vitro and in vivo antibacterial activity of novel macrolides against recent clinical isolates*. 6th Int Conf Macrolides Azalides Streptogramins Ketolides Oxazolidinones (Jan 23-25, Bologna) 2002, Abst 1.02.

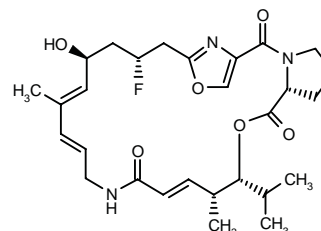
RPR-202868/RPR-132552³⁻¹¹

293723

Oral streptogramin composed of two semisynthetic synergistic components in a 30/70 w:w association: RPR-202868, a pristnamycin I derivative, and RPR-132552, a pristnamycin II derivative

RPR-132552^{*,1} 299674

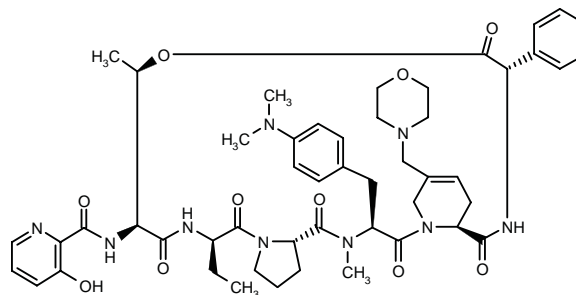
16-Deoxo-16(*R*)-fluoropristnamycin II_B



C28 H38 F N3 O6; Mol wt: 531.6212

RPR-202868^{**,2} 301114

5-[(2*S*)-1,2,3,6-Tetrahydro-5-(4-morpholinylmethyl)-2-pyridinecarboxylic acid]pristnamycin I_A



C50 H63 N9 O10; Mol wt: 950.1007

ACTION – Streptogramin antibiotic with broad-spectrum antibacterial activity against Gram-positive cocci, fastidious Gram-negative pathogens causing respiratory tract infections and anaerobes, and considered to have potential in the treatment of community-acquired infections. The combination showed rapid and potent bactericidal activity and exhibited an *in vitro* postantibiotic effect against *Staphylococcus aureus*, *Enterococcus faecium*, *Haemophilus influenzae* and *Streptococcus pneumoniae*, possibly due to irreversible binding to bacterial ribosome. Resistant mutants of *S. aureus* were isolated at a low frequency following exposure to 2 and 4 times the MIC of RPR-202868 alone and in combination with RPR-132552, but not at 8 times the MIC and not to RPR-132552; resistance to RPR-202868 was associated with erythromycin resistance. *In vivo*, oral administration of 120 mg/kg exhibited strong bactericidal activity in lungs of mice infected with *S. pneumoniae* and a dose of 50 mg/kg b.i.d. p.o. for 3 days significantly increased survival time compared to untreated infected animals. Compound was also active in experimental infections in mice caused by methicillin-resistant *S. aureus* and MLS_B-sensitive or -resistant *S. aureus*.

SOURCE – Aventis Pharma.

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- Berthaud, N. et al. *RPR202868/RPR132552, a new oral streptogramin: In vitro bacteriostatic activity*. 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst F-1835.
- Berthaud, N. et al. *RPR202868/RPR132552, a new oral streptogramin: In vivo efficacy against experimental Staphylococcus aureus infections in mice*. 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst F-1838.
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- Dutka Malen, S. et al. *RPR202868/RPR132552, a new oral streptogramin: In vitro selection of resistant mutants*. 41st Intersci Conf Antimicrob Agents Chemother (Dec 16-19, Chicago) 2001, Abst F-362.

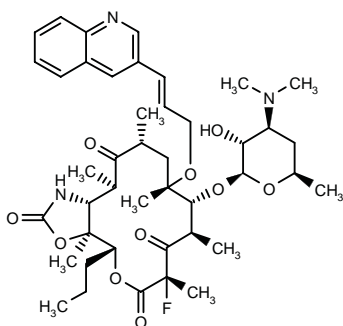
*Identified compound **299674** Drug Data Rep 2001, 023(06): 0572.

Identified compound **301114 Drug Data Rep 2001, 023(07): 0682.

RWJ-415663

313043

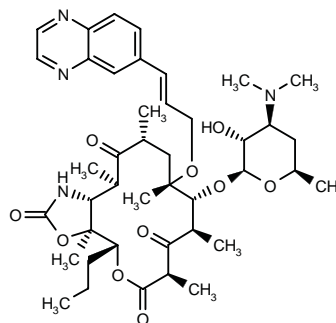
11-Amino-11-deoxy-3-des(hexopyranosyloxy)-2-fluoro-15-methyl-3-oxo-6-O-[3-(3-quinolyl)-2(E)-propenyl]-erythromycin A 11-N,12-O-cyclic carbamate



C43 H60 F N3 O10; Mol wt: 797.9560

ACTION – Ketolide antibiotic, an erythromycin A analogue with antibacterial activity comparable to the reference compounds telithromycin and ABT-773, giving MIC values of 0.12 µg/ml against macrolide-susceptible and -resistant streptococci and macrolide-susceptible and inducibly resistant staphylococci. In mice, compound protected against systemic infections caused by *Staphylococcus*

aureus or *Streptococcus pneumoniae*, with ED₅₀ values of 5 and 6 mg/kg s.c., respectively, compared to respective ED₅₀ values of 5 and 8 mg/kg s.c. for ABT-773 and 5 and 13 mg/kg s.c. for telithromycin. Compound was also active after oral administration (ED₅₀ = 6 mg/kg in an *S. pneumoniae* infection model) and exhibited a favorable oral pharmacokinetic profile, with C_{max} and AUC values comparable to telithromycin and about 3-fold higher than ABT-773, and a plasma AUC/MIC ratio comparable to ABT-773 and superior to telithromycin. Another related compound is:



RWJ-415667 [313046]: C42 H60 N4 O10

SOURCES – Kosan; R.W. Johnson.

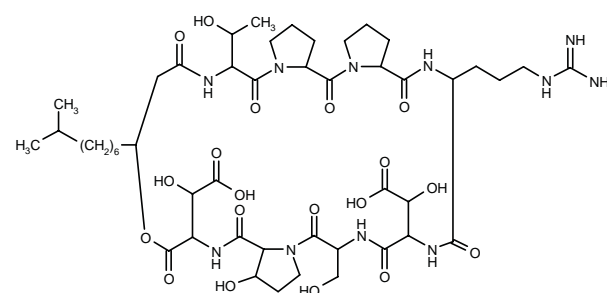
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- Bush, K. et al. *In vitro and in vivo microbiological activities of ketolides derived from 15-methylerythromycin A*. 6th Int Conf Macrolides Azalides Streptogramins Ketolides Oxazolidinones (Jan 23-25, Bologna) 2002, Abst 1.06.
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TRIPROPEPTIN Z

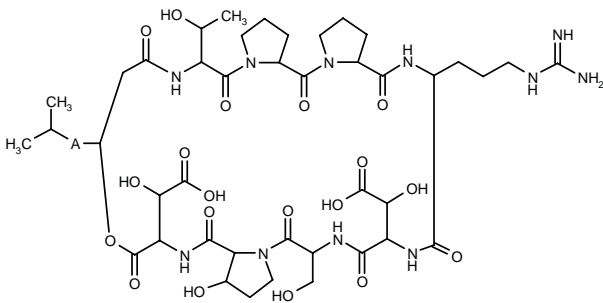
311448

3-Hydroxy-10-methylundecanoyl-DL-threonyl-DL-prolyl-DL-prolyl-DL-arginyl-3-hydroxy-DL-aspartyl-DL-seryl-4-hydroxy-DL-prolyl-3-hydroxy-DL-aspartic acid C-1.9-O-3.1-lactone



C48 H77 N11 O19; Mol wt: 1112.1940

ACTION – Macrocyclic antibiotic isolated from a culture of *Lysobacter* sp. BMK333-48F3 (FERM BP-7477), with antibacterial activity against a panel of microorganisms including resistant strains. Other compounds from the same source are:



Compound	A	Formula
Tripropeptin A [311450]	-(CH2)7-	C ₄₉ H ₇₉ N ₁₁ O ₁₉
Tripropeptin B [311451]	-(CH2)8-	C ₅₀ H ₈₁ N ₁₁ O ₁₉
Tripropeptin C [311452]	-(CH2)9-	C ₅₁ H ₈₃ N ₁₁ O ₁₉
Tripropeptin D [311453]	-(CH2)10-	C ₅₂ H ₈₅ N ₁₁ O ₁₉

SOURCE – Microbial Chemistry Research Foundation, Tokyo (JP).

REFERENCES

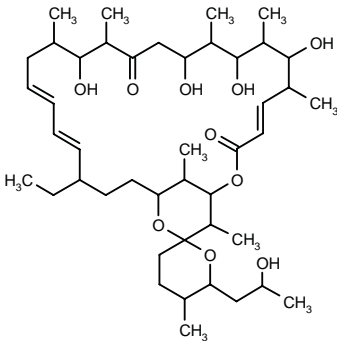
1. Takeuchi, T. et al. (Microbial Chemistry Research Foundation) *Antibiotics tripropeptins and process for producing the same*. WO 0174850.

2. Hashizume, H. et al. *Tripropeptins, novel antimicrobial agents produced by Lysobacter sp. I. Taxonomy, isolation ad biological activities*. J Antibiot 2001, 54(12): 1054.

WK-6150

310681

22-Ethyl-7,9,11,15-tetrahydroxy-6'-(2-hydroxypropyl)-5',6,8,10,14,16,28,29-octamethylspiro[2,26-dioxabicyclo[23.3.1]nonacosa-4,18,20-triene-27,2'-tetrahydropyran]-3,13-dione



C44 H74 O10; Mol wt: 763.0586

ACTION – Antibiotic isolated from *Streptomyces* sp. WK-6150 (FERM BP-7036) with *in vitro* activity against a panel of bacterial strains.

SOURCE – Kitasato Institute, Tokyo (JP).

REFERENCES

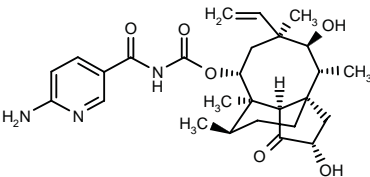
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ANTIBACTERIAL DRUGS

311635

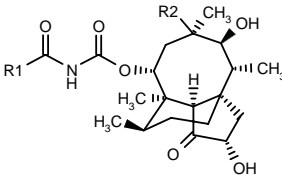
N-(6-Aminopyridin-3-ylcarbonyl)carbamic acid (2*S*,3*aS*,4*R*,5*S*,6*S*,8*R*,9*R*,9*aR*,10*R*)-2,5-dihydroxy-4,6,9,10-tetramethyl-1-oxo-6-vinylperhydro-3*a*,9-propano-cyclopentacycloocten-8-yl ester

14-*O*-[*N*-(6-Aminopyridin-3-ylcarbonyl)carbamoyl]-2(*S*)-hydroxymutilin



C27 H37 N3 O6; Mol wt: 499.6043

ACTION – Antibacterial mutilin derivative active against Gram-positive and Gram-negative bacteria and *Mycoplasma* including *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Enterococcus faecalis*, *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus pneumoniae*, *Haemophilus* spp., *Neisseria* spp., *Legionella*, spp., *Chlamydia* spp., *Moraxella catarrhalis*, *Mycoplasma pneumoniae* and *Mycoplasma gallisepticum*. By virtue of its activity against *Chlamydia pneumoniae*, the compound is also expected to be useful for the treatment of bacteria-induced atherosclerosis. Other specifically claimed 2-hydroxymutilin carbamates include the following:



Compound	R1	R2	Formula
311636	6-Me-3-pyridazinyl	vinyl	C ₂₇ H ₃₇ N ₃ O ₆
311637	2-[1-(CNCH2)-4-Pip]-4-thiazolyl	vinyl	C ₃₂ H ₄₄ N ₄ O ₆ S
311638	3-oxo-3,4-dihydro-pyrido[2,3-b]pyrazin-7-yl	Et	C ₂₉ H ₃₈ N ₄ O ₇
311639	2-NH2-6-MeO-4-pyrimidinyl	vinyl	C ₂₇ H ₃₈ N ₄ O ₇
311640	4-NH2-6-MeO-3-Pyr	vinyl	C ₂₈ H ₃₉ N ₃ O ₇
311641	6-NH2-3-Pyr	Et	C ₂₇ H ₃₉ N ₃ O ₆
311642	6-NH2-3-pyridazinyl	vinyl	C ₂₆ H ₃₆ N ₄ O ₆

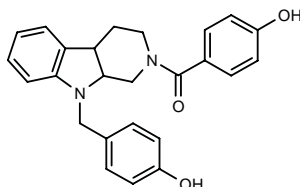
SOURCE – GlaxoSmithKline.

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313047

4-[2-(4-Hydroxybenzoyl)-1,2,3,4,4a,9a-hexahydro-9H- β -carbolin-9-ylmethyl]phenol



C25 H24 N2 O3; Mol wt: 400.4756

ACTION – Antibacterial agent, an inhibitor of the enoyl acyl carrier protein reductase FabI, with respective IC_{50} values of 0.15 and 4.2 μ g/ml against *Staphylococcus aureus* and *Escherichia coli* FabI; it was inactive against human FAB at concentrations up to 100 μ g/ml. Compound was active *in vitro* against *S. aureus* (MIC = 0.5 μ g/ml).

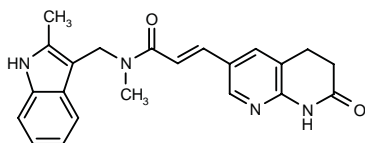
SOURCE – GlaxoSmithKline.

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313048

N-Methyl-N-(2-methyl-1H-indol-3-ylmethyl)-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)-2(E)-propenamide



C22 H22 N4 O2; Mol wt: 374.4418

ACTION – Antibacterial agent, an inhibitor of the enoyl acyl carrier protein reductase FabI, proven to inhibit *Staphylococcus aureus* FabI, *Haemophilus influenzae* FabI and *Streptococcus pneumoniae* FabK with IC_{50} values of 0.03, 0.13 and 3.0 μ M, respectively; it was inactive against human fatty acid biosynthesis (IC_{50} > 100 μ M) and was not cytotoxic to human lung carcinoma A549 cells (IC_{50} > 200 μ M). Compound exhibited broad-spectrum activity against Gram-positive and Gram-negative bacteria including *S. aureus* (MIC = 0.06 μ g/ml or less), *H. influenzae* (MIC = 1-2 μ g/ml), *Moraxella catarrhalis* (MIC = 0.06 μ g/ml or less), *Escherichia coli* (MIC = 0.5 μ g/ml), *Enterococcus faecalis* (MIC = 16 μ g/ml) and *S. pneumoniae* (MIC = 8-16 μ g/ml), and it was highly active against methicillin-resistant *S. aureus* (MRSA; MIC = 0.06 μ g/ml or less). *In vivo* in an MRSA groin abscess model in rats, compound at a dose of 50 mg/kg p.o. reduced bacterial counts by 3.5 \log_{10} and its activity was comparable to amoxicillin/clavulanic acid (350/50 mg/kg).

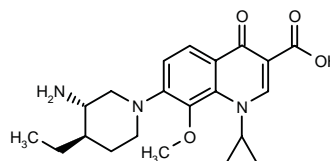
SOURCE – GlaxoSmithKline.

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2. Seefeled, M.A. et al. *Discovery and characterization of highly potent naphthyridine-based FabI inhibitors with in vivo activity*. 41st Intersci Conf Antimicrob Agents Chemother (Dec 16-19, Chicago) 2001, Abst F-1690.

313068

7-[3(S)-Amino-4(R)-ethylpiperidin-1-yl]-1-cyclopropyl-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid



C21 H27 N3 O4; Mol wt: 385.4613

ACTION – Antibacterial agent, a nonfluorinated quinolone with broad-spectrum antibacterial activity against Gram-positive and Gram-negative bacteria including *Staphylococcus aureus*, *Streptococcus pneumoniae* and *Escherichia coli* (MIC = 0.008 mg/l or less), as well as quinolone-resistant *S. aureus* and *Pseudomonas aeruginosa* (MIC = 0.06 and 0.5 mg/l, respectively).

SOURCE – Procter & Gamble.

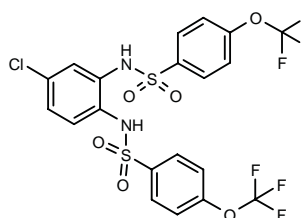
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A-358

301546

N,N'-(4-Chloro-1,2-phenylene)bis[4-(trifluoromethoxy)-benzenesulfonamide]



C20 H13 Cl F6 N2 O6 S2; Mol wt: 590.9037

ACTION – Antibacterial agent, an inhibitor of dehydroquinase synthase (DHQS; $IC_{50} = 3 \mu M$) with good activity against Gram-positive bacteria including susceptible and resistant strains of *Staphylococcus aureus*, *Corynebacterium* spp., *Enterococcus* spp., *Propionibacterium* spp. and β -hemolytic streptococci (MIC = 1.4-8 $\mu g/ml$), but little or no activity against Gram-negative bacteria. In time-kill experiments, A-358 showed concentration-dependent killing of *S. aureus* and no drug-resistant mutants have been obtained. Topically administered compound significantly reduced skin carriage of *S. aureus* in a mouse model of skin colonization with *S. aureus*; it was 10-fold more effective than *Bactroban* (mupirocin), and its antimicrobial activity appeared to be localized to the skin.

SOURCE – Arrow Therapeutics.

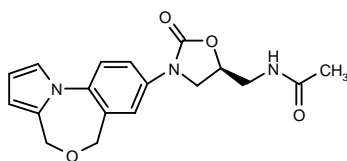
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- Arrow Therapeutics' novel antibiotic enters full development. DailyDrugNews.com (Daily Essentials) 2001, Dec 30.

ABX-96

312531

N-[3-(4,6-Dihydropyrrolo[1,2-a][4,1]benzoxazepin-8-yl)-2-oxooxazolidin-5(S)-ylmethyl]acetamide



C18 H19 N3 O4; Mol wt: 341.3651

ACTION – Oxazolidinone antibacterial agent with broad-spectrum activity against both sensitive and resistant Gram-positive bacteria including methicillin-sensitive and -resistant *Staphylococcus aureus*, vancomycin-sensitive and -resistant *Enterococcus faecalis*, and vancomycin-resistant *Enterococcus faecium* (MIC = 2 $\mu g/ml$). Compound exhibited a good pharmacokinetic profile after oral administration in rats and good efficacy in protecting mice against systemic infections produced by *S. aureus* ($ED_{50} = 10.1$ and 12.5 mg/kg s.c. and p.o., respectively).

SOURCE – Dr. Reddy's Research Foundation.

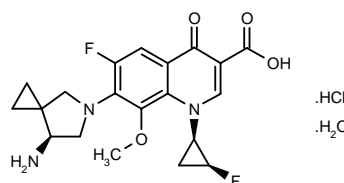
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DK-507k

311610

7-[7(S)-Amino-5-azaspiro[2.4]hept-5-yl]-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid hydrochloride hydrate



C20 H21 F2 N3 O4 . HCl . H2O; Mol wt: 459.8746

ACTION – Quinolone antibacterial with broad-spectrum antibacterial activity against sensitive and resistant Gram-positive and Gram-negative pathogens including penicillin-resistant *Streptococcus pneumoniae* (MIC₉₀ = 0.12 $\mu g/ml$), ciprofloxacin-susceptible/methicillin-resistant *Staphylococcus aureus* (MIC₉₀ = 0.006 $\mu g/ml$), penicillin-susceptible or -resistant *S. pneumoniae* (MIC₉₀ = 0.12 $\mu g/ml$), methicillin-resistant coagulase-negative staphylococci (MIC₉₀ = 0.5 $\mu g/ml$) and ciprofloxacin-susceptible *Pseudomonas aeruginosa* (MIC = 1 $\mu g/ml$). In mice with septicemia caused by sensitive or resistant strains of *S. aureus* or *S. pneumoniae*, or pneumonia caused by penicillin-resistant *S. pneumoniae*, compound exhibited strong efficacy after oral administration ($ED_{50} = 9.5-15$ mg/kg) and was more active than gatifloxacin, moxifloxacin and levofloxacin. It had favorable physico-chemical, pharmacokinetic and toxicological profiles; it was absorbed rapidly after oral administration in rats and monkeys, showed relatively low plasma protein binding rates in rats (approximately 40%) and was excreted in the bile and feces. Moreover, no genotoxicity, phototoxicity, chondrotoxicity, cardiotoxicity or proconvulsant activity was observed.

SOURCE – Daiichi Pharmaceutical.

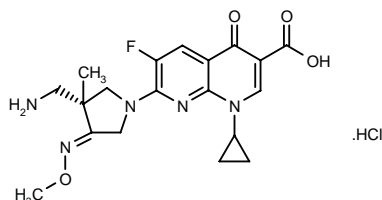
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- Kawakami, K. et al. *DK-570k, a new 8-methoxyquinolone: Synthesis and biological evaluation of 7-[(3-amino-4-substituted)pyrrolidin-1-yl] derivatives*. 41st Intersci Conf Antimicrob Agents Chemother (Dec 16-19, Chicago) 2001, Abst F-546.
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DW-286

312465

7-[3(*R*)-(Aminomethyl)-4(*Z*)-(methoxyimino)-3-methylpyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid hydrochloride



C19 H22 F N5 O4 . HCl; Mol wt: 439.8727

ACTION – Fluoronaphthyridone antibacterial agent with broad-spectrum activity against Gram-positive and Gram-negative bacteria, and superior *in vitro* activity compared to gemifloxacin, sparfloxacin and ciprofloxacin against Gram-positive pathogens, especially ofloxacin- and methicillin-resistant *Staphylococcus aureus* (MIC = 0.098 and < 0.002 µg/ml, respectively). The *in vivo* activity of compound against murine systemic infections reflects its *in vitro* activity; it was strongly active and more effective than gemifloxacin, sparfloxacin and ciprofloxacin against infections induced by Gram-positive bacteria (PD₅₀ = 0.2 and 0.12 mg/kg against susceptible and resistant *S. aureus*, respectively). Pharmacokinetic studies in mice, rats and dogs showed rapid absorption, with peak plasma levels and AUC significantly higher than those of ciprofloxacin.

SOURCE – Dong-Wha.

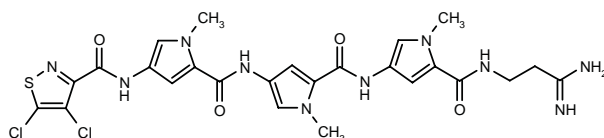
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GSQ-1530

312590

N-[5-[*N*-[5-[*N*-[5-[*N*-(2-Amidinoethyl)carbamoyl]-1-methyl-1*H*-pyrrol-3-yl]carbamoyl]-1-methyl-1*H*-pyrrol-3-yl]carbamoyl]-1-methyl-1*H*-pyrrol-3-yl]-4,5-dichloroisothiazole-3-carboxamide



C25 H26 Cl2 N10 O4 S; Mol wt: 633.5184

ACTION – Antibacterial agent, a *Hetero Aromatic Polycycle* (HARP) that binds to double-stranded DNA and interferes with bacterial DNA replication and RNA transcription. Compound exhibited antibacterial activity against Gram-positive organisms including methicillin-susceptible and -resistant *Staphylococcus aureus* (MIC₉₀ = 2 and 4 µg/ml, respectively), penicillin-resistant *Streptococcus pneumoniae* (MIC₉₀ = 2 µg/ml) and methicillin-susceptible and -resistant *Staphylococcus epidermidis* (MIC₉₀ = 2 µg/ml); poor activity was seen against wild-type Gram-negative microorganisms, excluding an *Escherichia coli* mutant (MIC = 0.5 µg/ml). Compound exhibited a bactericidal effect against streptococci and staphylococci and a bacteriostatic effect against enterococci; no crossresistance and no synergy or antagonism of the effect of other antibiotics was seen.

SOURCE – Genesoft.

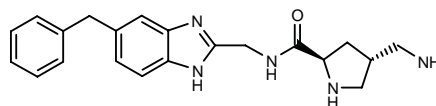
REFERENCES

- Ge, Y. et al. (Genesoft, Inc.) *Charged cpds. comprising a nucleic acid binding moiety and uses therefor*. WO 0174898.
- Burli, R. et al. *HARP: A novel class of antibiotics*. 41st Intersci Conf Antimicrob Agents Chemother (Dec 16-19, Chicago) 2001, Abst F-1685.
- Ge, Y. et al. *Evaluating in vitro potency of GSQ1530, a new class antibiotic HARP*. 41st Intersci Conf Antimicrob Agents Chemother (Dec 16-19, Chicago) 2001, Abst F-1687.

MC-04,112

312463

4(*R*)-(Aminomethyl)-*N*-(5-benzyl-1*H*-benzimidazol-2-ylmethyl)pyrrolidine-2(*R*)-carboxamide



C21 H25 N5 O; Mol wt: 363.4625

ACTION – Broad-spectrum efflux pump inhibitor able to induce 8-fold potentiation of the activity of levofloxacin against *Pseudomonas aeruginosa* at 10 µg/ml. Compound showed low cytotoxicity in K-562 cells (TC₅₀ = 275 µM) and the minimum lethal dose in mice was 70 mg/kg i.v.

SOURCES – Daiichi Pharmaceutical; Essential Therapeutics.

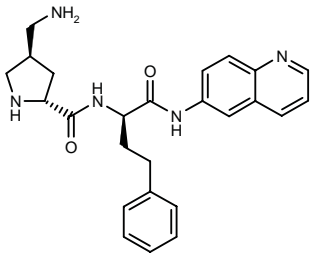
REFERENCES

- Zhang, J.Z. et al. *2-(Aminoalkyl)benzimidazoles - A class of broad-spectrum efflux pump inhibitors that potentiate the activity of levofloxacin in Pseudomonas aeruginosa*. 41st Intersci Conf Antimicrob Agents Chemother (Dec 16-19, Chicago) 2001, Abst F-342.

MC-04,124

311645

4(*R*)-(Aminomethyl)-D-prolyl-3-benzyl-D-alanine 6-quinolin-ylamide



C25 H29 N5 O2; Mol wt: 431.5371

ACTION – Broad-spectrum efflux pump inhibitor proven to potentiate the activity of macrolides against Gram-negative bacteria; for example, it potentiated the activity of levofloxacin against *Pseudomonas aeruginosa* by 8-fold at a concentration of 10 µg/ml. Compound exhibited low systemic toxicity in mice, with a minimum lethal dose of 100 mg/kg i.v., and high tissue/serum concentration ratios following i.v. dosing in rats. In murine Gram-negative infection models such as neutropenic mice with thigh infection caused by a strain of *P. aeruginosa* over-expressing the MexAB-OprM efflux pump, and mice with pyelonephritis caused by an *Escherichia coli* strain overexpressing the AcrAB efflux pump, the addition of compound (25-50 mg/kg i.p.) significantly enhanced the activity of levofloxacin and azithromycin compared to the antibiotics alone.

SOURCE – Essential Therapeutics.

REFERENCES

1. Cho, D. et al. *An efflux pump inhibitor (EPI), MC-04,124, enhances the activity of macrolides against Gram-negative bacteria.* 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst F-1497.

2. Griffith, D.C. et al. *Potential of levofloxacin and azithromycin by MC-04,124, a broad-spectrum efflux pump inhibitor, in mouse models of infection due to strains of Pseudomonas aeruginosa and Escherichia coli expressing efflux-pumps.* 41st Intersci Conf Antimicrob Agents Chemother (Dec 16-19, Chicago) 2001, Abst F-340.

3. Renau, T.E. and Lemoine, R.C. *Efflux pump inhibitors to address bacterial and fungal resistance.* Drugs Fut 2001, 26(12): 1171.

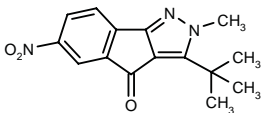
4. Renau, T.E. et al. *Conformationally restricted analogs of efflux pump inhibitors that potentiate the activity of levofloxacin in Pseudomonas aeruginosa.* 41st Intersci Conf Antimicrob Agents Chemother (Dec 16-19, Chicago) 2001, Abst F-341.

5. Watkins, W.J. et al. *The relationship between physicochemical properties, in vitro activity and pharmacokinetic profiles of analogs of the efflux pump inhibitor MC-04,124.* 41st Intersci Conf Antimicrob Agents Chemother (Dec 16-19, Chicago) 2001, Abst F-339.

MC-210,375^{1,3}

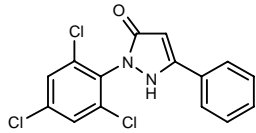
312461

3-*tert*-Butyl-2-methyl-6-nitroindeno[1,2-*c*]pyrazol-4(2*H*)-one

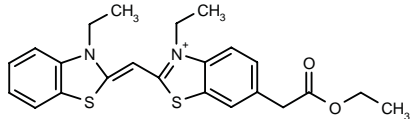


C15 H15 N3 O3; Mol wt: 285.3015

ACTION – Efflux pump inhibitor with high selectivity for the MexEF-OprN multidrug resistance (MDR) transporter from *Pseudomonas aeruginosa*. Compound was shown to potentiate the activity of levofloxacin only against strains of *P. aeruginosa* expressing the corresponding efflux pump. Other related compounds are:



MC-002,785 [311648]:^{1,2} C15 H9 Cl3 N2 O



MC-274,525 [312462]:¹ C23 H25 N2 O2 S2

SOURCES – Daiichi Pharmaceutical; Essential Therapeutics.

REFERENCES

1. Mao, W. et al. *Use of pump-selective inhibitors to discriminate between the specific mechanisms of efflux-mediated levofloxacin resistance in Pseudomonas aeruginosa.* 41st Intersci Conf Antimicrob Agents Chemother (Dec 16-19, Chicago) 2001, Abst F-343.

2. Renau, T.E. and Lemoine, R.C. *Efflux pump inhibitors to address bacterial and fungal resistance.* Drugs Fut 2001, 26(12): 1171.

3. Warren, M. et al. *Characterization of a MexEF-OprN-selective efflux pump inhibitor using fluorescence-based accumulation assays.* 41st Intersci Conf Antimicrob Agents Chemother (Dec 16-19, Chicago) 2001, Abst F-344.

PISCIDIN 1

311107

L-Phenylalanyl-L-phenylalanyl-L-histidyl-L-histidyl-L-isoleucyl-L-phenylalanyl-L-arginyl-glycyl-L-isoleucyl-L-valyl-L-histidyl-L-valyl-glycyl-L-lysyl-L-threonyl-L-isoleucyl-L-histidyl-L-arginyl-L-leucyl-L-valyl-L-threonyl-glycine

C122 H187 N37 O25; Mol wt: 2572.0530

ACTION – Antimicrobial peptide isolated from the mast cells of a hybrid striped bass, with potent and broad-spectrum antibacterial activity, which appeared to be correlated with its hemolytic activity. Other peptides are:

L-Phenylalanyl-L-phenylalanyl-L-histidyl-L-histidyl-L-isoleucyl-L-phenylalanyl-L-arginyl-glycyl-L-isoleucyl-L-valyl-L-histidyl-L-valyl-glycyl-L-lysyl-L-threonyl-L-isoleucyl-L-histidyl-L-lysyl-L-leucyl-L-valyl-L-threonyl-glycine

Piscidin 2 [311108]: C122 H187 N35 O25

L-Phenylalanyl-L-isoleucyl-L-histidyl-L-histidyl-L-isoleucyl-L-phenylalanyl-L-arginyl-glycyl-L-isoleucyl-L-valyl-L-histidyl-L-alanyl-glycyl-L-arginyl-L-seryl-L-isoleucyl-glycyl-L-arginyl-L-phenylalanyl-L-leucyl-L-threonyl-glycine

Piscidin 3 [311109]: C116 H179 N37 O25

SOURCE – North Carolina State University, Raleigh, NC (US).

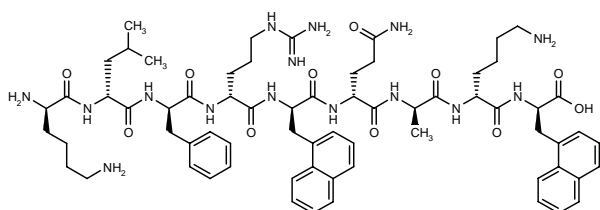
REFERENCES

1. Noga, E.J. and Silphaduang, U. *Peptide antibiotics in mast cells of fish*. Nature 2001, 414268.

XMP-629

313006

D-Lysyl-D-leucyl-D-phenylalanyl-D-arginyl-3-(1-naphthyl)-D-alanyl-D-glutaminy-D-alanyl-D-lysyl-3-(1-naphthyl)-D-alanine



C67 H93 N15 O11; Mol wt: 1284.5660

ACTION – Antibacterial agent, a low-molecular-weight peptide derived from functional domain II of human bactericidal/permeability-increasing protein (BPI), with broad-spectrum activity against clinically relevant organisms including *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Candida albicans*. *In vivo* in models of acute peritonitis and endotoxemia in mice, compound at doses of 1-10 mg/kg i.p. produced a significant increase in survival compared with control animals.

SOURCE – Xoma.

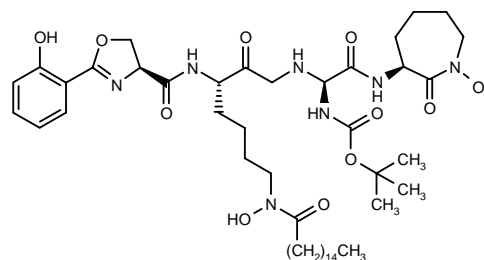
REFERENCES

1. Little, R.G. et al. (Xoma [US] LLC) *Therapeutic peptide-based constructs*. WO 0100655.
2. Lim, F. et al. *XMP-629, a peptide derived from functional domain II of BPI demonstrates broad-spectrum antimicrobial and endotoxin neutralizing properties in vitro and in vivo*. 41st Intersci Conf Antimicrob Agents Chemother (Dec 16-19, Chicago) 2001, Abst F-346.

ANTIMYCOBACTERIAL AGENTS

311398

N-[1(*S*)-[2-[1(*R*)-(tert-Butoxycarbonylamino)-2-[1-hydroxy-2-oxoperhydroazepin-3(*S*)-ylamino]-2-oxoethylamino]-acetyl]-5-(*N*-hexadecanoyl-*N*-hydroxyamino)pentyl]-2-(2-hydroxyphenyl)-4,5-dihydrooxazole-4(*S*)-carboxamide



C46 H75 N7 O11; Mol wt: 902.1365

ACTION – A representative compound from a series of 1-hydroxy-2-oxoperhydro-1,4-azepine derivatives with antimycobacterial activity, particularly useful for the treatment of *Mycobacterium tuberculosis* infections.

SOURCE – University of Notre Dame, Notre Dame, IN (US).

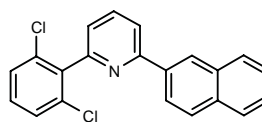
REFERENCES

1. Miller, M.J. and Xu, Y. (University of Notre Dame) *Antimycobacterial agents*. US 6310058.

ANTIFUNGAL AGENTS

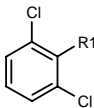
311147

2-(2,6-Dichlorophenyl)-6-(2-naphthyl)pyridine



C21 H13 Cl2 N; Mol wt: 350.2467

ACTION – Antifungal agent with MIC values of 0.3 and 1 µg/ml against *Botrytis cinerea* and *Trichophyton mentagrophytes*, respectively. Compound was able to inhibit the accumulation of squalene in *B. cinerea* cells by 90% at 30 µM, indicating squalene epoxidase-inhibitory properties. Other exemplified heterocyclic compounds are:



Compound	R1	Formula
311148	6-(4-Cl-Ph)-2-Pyr	C ₁₇ H ₁₀ Cl ₃ N
311150	2-(2-Naph)-4-thiazolyl	C ₁₉ H ₁₁ Cl ₂ NS
311151	4-(2-Naph)-5,6-dihydro-4H-1,3-oxazin-2-yl	C ₂₀ H ₁₅ Cl ₂ NO

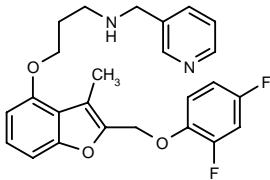
SOURCE – Nippon Soda.

REFERENCES

1. Kumida, I. and Noda, K. (Nippon Soda Co., Ltd.) *Nitrogen-containing heterocyclic cpds. and bactericidal agents.* JP 2001261648.

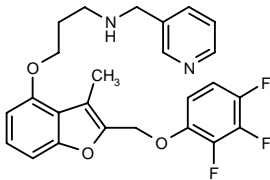
311280

N-[3-[2-(2,4-Difluorophenoxy)methyl]-3-methyl-1-benzofuran-4-yloxy]propyl]-*N*-(pyridin-3-ylmethyl)amine



C25 H24 F2 N2 O3; Mol wt: 438.4716

ACTION – Antifungal agent, a potent and selective inhibitor of *Candida albicans* *N*-myristoyltransferase (IC₅₀ = 7.5 nM; IC₅₀ > 450 μM against human enzyme) with potent antifungal activity *in vitro* against *C. albicans* CY1002 (IC₅₀ = 0.035 μM in the absence of serum; IC₅₀ = 0.33 μM in the presence of serum). The compound also showed *in vivo* activity and favorable pharmacokinetics in rats. Another related compound is:



311281: C25 H23 F3 N2 O3

SOURCE – Nippon Roche.

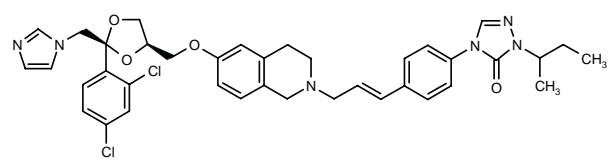
REFERENCES

1. Aoki, Y. et al. (F. Hoffmann-La Roche AG) *Novel bicyclic cpds.* WO 0037464.

2. Masubuchi, M. et al. *Design and synthesis of a new class of antifungal agents targeting fungal N-myristoyltransferase.* 21st Symp Med Chem (Nov 28-30, Kyoto) 2001, Abst 1P-05.

311572

cis-4-[4-[3-[6-[2-(2,4-Dichlorophenyl)-2-(1*H*-imidazol-1-ylmethyl)-1,3-dioxolan-4-ylmethoxy]-1,2,3,4-tetrahydroisoquinolin-2-yl]-1(*E*)-propenyl]phenyl]-2-(1-methylpropyl)-3,4-dihydro-2*H*-1,2,4-triazol-3-one



C38 H40 Cl2 N6 O4; Mol wt: 715.6780

ACTION – A representative compound from a series of 1,2,3,4-tetrahydroisoquinoline derivatives with antifungal activity, active against *Candida* spp. including *Candida albicans*, *Candida glabrata*, *Candida krusei*, *Candida tropicalis*, *Candida pseudotropicalis* and *Candida parapsilosis*, and also against *Aspergillus fumigatus*, *Aspergillus flavus*, *Aspergillus niger*, *Cryptococcus neoformans*, *Microsporum canis*, *Trichophyton rubrum* and *Trichophyton mentagrophytes*.

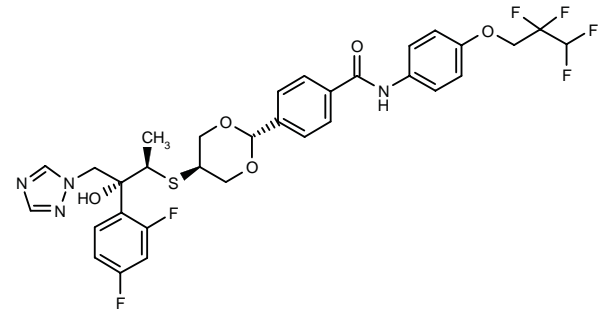
SOURCE – Aventis Pharma.

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1. Babin, D. et al. (Aventis Pharma SA) *Novel 1,2,3,4-tetrahydroisoquinoline, their preparation method and their use as fungicides.* WO 0174808.

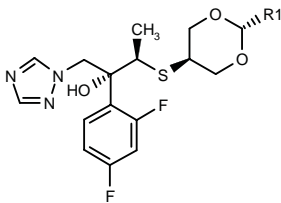
311605

trans-4-[5-[2(*R*)-(2,4-Difluorophenyl)-2-hydroxy-1(*R*)-methyl-3-(1*H*-1,2,4-triazol-1-yl)propylsulfanyl]-1,3-dioxan-2-yl]-*N*-[4-(2,2,3,3-tetrafluoropropoxy)phenyl]benzamide



C32 H30 F6 N4 O5 S; Mol wt: 696.6660

ACTION – Antifungal agent with MIC values of 0.016, 0.063 and 0.125 μg/ml, respectively, against *Candida albicans* SANK 51486, *Cryptococcus neoformans* TIMM 1855 and *Aspergillus fumigatus* SANK 10569. Other exemplified triazole derivatives include the following:



Compound	R1	Formula
311606	6-(4-CN-PhNHCO)-2-Naph	C ₃₄ H ₂₉ F ₂ N ₅ O ₄ S
311607	3-(4-Cl-PhNHCO)-Ph	C ₂₉ H ₂₇ ClF ₂ N ₄ O ₄ S
311608	4-(4-OH-PhNHCO)-Ph	C ₂₉ H ₂₈ F ₂ N ₄ O ₅ S
311609	4-(4-CN-PhCH ₂ NHCO)-Ph	C ₃₁ H ₂₉ F ₂ N ₅ O ₄ S

SOURCE – Sankyo.

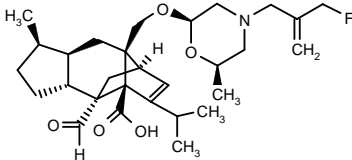
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1. Uchida, T. and Konosu, T. (Sankyo Co., Ltd.) *Triazole cpds. having amide linkage*. JP 2001342187, WO 0172743.

GW-587270^{1,4}

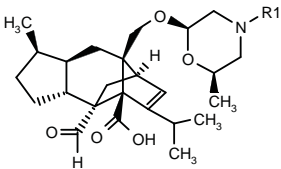
311883

[1 *R*-(1 α ,3 α ,4 α ,4 α ,7 β ,7 α ,8 α)]-8a-[4-[2-(Fluoromethyl)-2-propenyl]-6(*R*)-methylmorpholin-2(*R*)-yloxymethyl]-4-formyl-3-isopropyl-7-methyl-1,3a,4,4a,5,6,7,7a,8,8a-decahydro-1,4-methano-*s*-indacene-3a-carboxylic acid



C29 H42 F N O5; Mol wt: 503.6508

ACTION – Azasordarin antifungal agent with significant activity against clinically relevant *Candida* spp. such as *Candida albicans* (including fluconazole-resistant strains; MIC₉₀ = 0.015 μ g/ml), *Candida tropicalis* (MIC₉₀ = 0.06 μ g/ml) and *Candida glabrata* (MIC₉₀ = 0.5 μ g/ml). Compound was inactive against *Candida krusei* and *Cryptococcus neoformans*, but displayed excellent activity against *Pneumocystis carinii* (MIC₅₀ = 0.001 μ g/ml or less) and significant activity against emerging fungal pathogens affecting immunocompromised patients such as *Blastoschizomyces capitatus* and *Geotrichum clavatum* (MIC = 0.12 μ g/ml). The *in vitro* cytotoxic concentrations of compound against mammalian cell lines derived from target organs (liver, kidney, lung and brain) ranged from 49 to 62 μ g/ml. Other related compounds are:



Compound	R1	Formula
GW-471552 [294238] ^{1,4,7-11}	cyclopropyl	C ₂₈ H ₄₁ NO ₅
GW-471558 [294239] ¹⁻¹¹	allyl	C ₂₈ H ₄₁ NO ₅
GW-479821 [311880] ^{1,4}	4-MeO-PhCH ₂	C ₃₃ H ₄₅ NO ₆
GW-515716 [311881] ^{1,4}	CH ₂ C(Me)=CH ₂	C ₂₉ H ₄₃ NO ₅
GW-570009 [311882] ^{1,4}	CH ₂ CH=CH=CH ₂	C ₂₉ H ₄₁ NO ₅

SOURCE – GlaxoSmithKline.

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1. Bueno, J.M. et al. (Glaxo Wellcome SA) *Morpholino ethers*. EP 1077959, WO 9958512.

2. Aviles, P. et al. *Pharmacokinetic parameters of azasordarin derivatives (GW 471558 and GW 531920) after intravenous administration*. 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst J-1690.

3. Cuenca-Estrella, M. et al. *Azasordarins: Susceptibility of fluconazole-susceptible and fluconazole-resistant clinical isolates of Candida spp. to GW 471558*. Antimicrob Agents Chemother 2001, 45(6): 1905.

4. Herreros, E. et al. *Antifungal activities and cytotoxicity studies of six new azasordarins*. Antimicrob Agents Chemother 2001, 45(11): 3132.

5. Herreros, E. et al. *In vitro activity of azasordarins against clinical isolates of yeasts and filamentous fungi*. 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst J-201.

6. Herreros, E. et al. *Investigation of in vitro development of resistance to azasordarins in Candida albicans*. 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst J-202.

7. Herreros, E. et al. *Preliminary toxicology of azasordarins*. 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst J-1691.

8. Lozano-Chiu, M. et al. *Anti-Candida activity of the sordarin derivatives GW471552, GW471558, GW506540, GW531920, and GW560849: Effect of endpoint rule and incubation time on MIC*. 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst J-192.

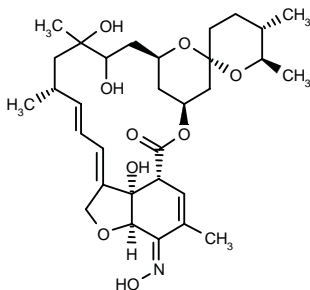
9. Martinez, A. et al. *Antifungal activities of two new azasordarins, GW471552 and GW471558, in experimental models of oral and vulvovaginal candidiasis in immunosuppressed rats*. Antimicrob Agents Chemother 2001, 45(12): 3304.

10. Martinez, A. et al. *Antifungal activity of azasordarins against oral and vaginal candidiasis in immunosuppressed rats*. 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst J-1689.

11. Martinez, A. et al. *In vivo activity of azasordarins against two rat models of pneumocystosis*. 40th Intersci Conf Antimicrob Agents Chemother (Sept 17-20, Toronto) 2000, Abst F-1096.

MC-05,686**312243***Mixture of two milbemycins:***314244**

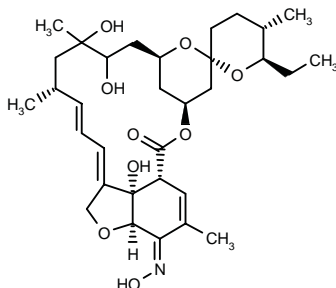
(5'*S*,6*R*,6'*R*,11*R*,13*R*,15*S*,17*aR*,20*aR*,20*bS*)-8,9,20*b*-Trihydroxy-5',6,6',8,19-pentamethyl-2,3',4',5',6,6',7,8,9,10,11,14,15,17*a*,20*a*,20*b*-hexadecahydrospiro[11,15-methanofuro[4,3,2-*pq*][2,6]benzodioxacyclooctadecin-13,2'-pyran]-17,20-dione 20-oxime



C31 H45 N O9; Mol wt: 575.6945

314245

(5'*S*,6*R*,6'*R*,11*R*,13*R*,15*S*,17*aR*,20*Z*,20*aR*,20*bS*)-6'-Ethyl-8,9,20*b*-trihydroxy-5',6,8,19-tetramethyl-2,3',4',5',6,6',7,8,9,10,11,14,15,17*a*,20*a*,20*b*-hexadecahydrospiro[11,15-methanofuro[4,3,2-*pq*][2,6]benzodioxacyclooctadecin-13,2'-pyran]-17,20-dione 20-oxime



C32 H47 N O9 Mol wt: 589.7213

ACTION – Antifungal agent, an efflux pump inhibitor that potentiates the activity of fluconazole, with an MPC₈ (minimum concentration of inhibitor required to decrease the MIC of fluconazole against *Candida albicans* 8-fold) of 0.5 µg/ml. Compared with the parent milbemycin K oxime (MPC₈ = 0.0625 µg/ml or less), compound was approximately 20-fold less cytotoxic against human chronic myeloid leukemia K-562 cells (CC₅₀ = 56 and 2.4 µg/ml, respectively).

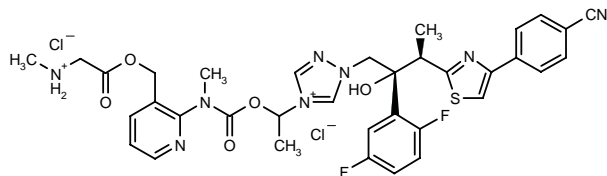
SOURCE – Essential Therapeutics.**REFERENCES**

1. Lemoine, R. et al. *The milbemycins as fungal efflux pump inhibitors (FEPIs): Decreased cytotoxicity and improved solubility*. 41st Intersci Conf Antimicrob Agents Chemother (Dec 16-19, Chicago) 2001, Abst F-2160.

2. Renau, T.E. and Lemoine, R.C. *Efflux pump inhibitors to address bacterial and fungal resistance*. *Drugs Fut* 2001, 26(12): 1171.

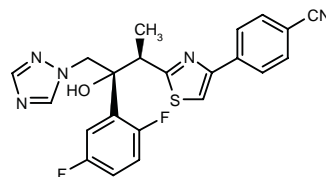
RO-0098557^{1,3,4}**311257**

1-[3(*R*)-[4-(4-Cyanophenyl)thiazol-2-yl]-2(*R*)-(2,5-difluorophenyl)-2-hydroxybutyl]-4-[1-[*N*-methyl-*N*-[3-[2-(methylammonio)acetoxymethyl]pyridin-2-yl]carbamoyloxy]ethyl]-1*H*-1,2,4-triazol-4-ium dichloride

BAL-8557

C35 H36 Cl2 F2 N8 O5 S; Mol wt: 789.6884

ACTION – Broad-spectrum antifungal agent, a quaternary ammonium salt prodrug of **Ro-0094815** with improved aqueous solubility (> 100 mg/ml vs. < 0.1 µg/ml) and strong *in vivo* antifungal activity in rat systemic candidiasis (ED₅₀ = 0.9-4.0 µmol/kg i.v., 0.8-4.0 µmol/kg p.o.) and in a rat model of pulmonary and systemic aspergillosis (ED₅₀ = 6.0-12 µmol/kg i.v., 8.9-14 µmol/kg p.o.).

**Ro-0094815 [281150]:^{*,1-4}** C22 H17 F2 N5 O S**SOURCES** – Basilea Pharmaceutica; Nippon Roche.**REFERENCES**

1. Fukuda, H. et al. (F. Hoffmann-La Roche AG) *N*-Substd. carbamoyloxyalkyl-azolium derivs. WO 0132652.

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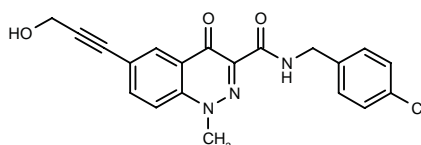
3. Ohwada, J. et al. *Development of novel water antifungal, RO0098557*. 21st Symp Med Chem (Nov 28-30, Kyoto) 2001, Abst 1P-06.

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^{*}Identified compound **281150** (see **281149**) Drug Data Rep 1999, 021(11): 0997.

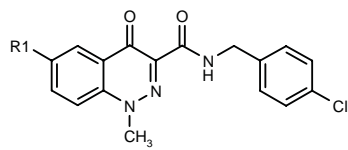
ANTIVIRAL DRUGS**310975**

N-(4-Chlorobenzyl)-6-(3-hydroxy-1-propynyl)-1-methyl-4-oxo-1,4-dihydrocinnoline-3-carboxamide



C20 H16 Cl N3 O3; Mol wt: 381.8174

ACTION – Antiviral agent particularly active against herpesviruses, giving IC₅₀ values of 2.7, 1.7 and 1.1 μM against cytomegalovirus (CMV), herpes simplex virus (HSV) and varizella-zoster virus (VZV) polymerases, respectively. Other exemplified 4-oxo-1,4-dihydrocin-noline-3-carboxamides include the following:



Compound	R1	Formula
310976	I	C ₁₇ H ₁₃ ClIN ₃ O ₂
310977	ethynylene-CH ₂ CH ₂ OH	C ₂₁ H ₁₈ ClN ₃ O ₃
310978	CH ₂ OH	C ₁₈ H ₁₆ ClN ₃ O ₃
310979	4-morpholinyl-CH ₂	C ₂₂ H ₂₃ ClN ₄ O ₃

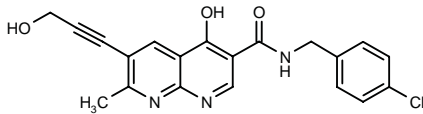
SOURCE – Pharmacia.

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1. Vaillancourt, V.A. et al. (Pharmacia Corp.) 4-Oxo-1,4-dihydro-3-cinnoline-carboxamides as antiviral agents. WO 0170706.

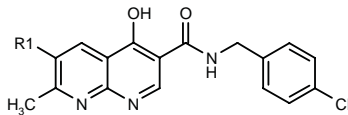
310980

N-(4-Chlorobenzyl)-4-hydroxy-6-(3-hydroxy-1-propynyl)-7-methyl-1,8-naphthyridine-3-carboxamide



C₂₀ H₁₆ Cl N₃ O₃; Mol wt: 381.8174

ACTION – Antiviral agent particularly active against herpesviruses, giving an IC₅₀ of 2.1 μM against cytomegalovirus (CMV) polymerase. Other exemplified 4-hydroxy-1,8-naphthyridine-3-carboxamides include the following:



Compound	R1	Formula
310981	H	C ₁₇ H ₁₄ ClN ₃ O ₂
310982	Br	C ₁₇ H ₁₃ BrClN ₃ O ₂
310983	I	C ₁₇ H ₁₃ ClIN ₃ O ₂
310984	CO ₂ Me	C ₁₉ H ₁₆ ClN ₃ O ₄

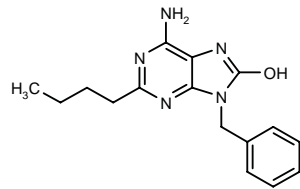
SOURCE – Pharmacia.

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1. Vaillancourt, V.A. (Pharmacia Corp.) 4-Hydroxy-1,8-naphthyridine-3-carboxamides as antiviral agents. WO 0170742.

311276

6-Amino-9-benzyl-2-butyl-9H-purin-8-ol



C₁₆ H₁₉ N₅ O; Mol wt: 297.3601

ACTION – Interferon inducer able to increase interferon levels *in vitro* in murine spleen cells (minimum effective concentration = 0.03 μM) and *in vivo* in mice (minimum effective dose = 0.3 mg/kg p.o.). Potentially useful for the treatment of hepatitis C virus (HCV) infection.

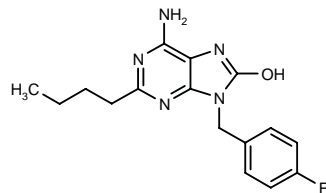
SOURCES – Japan Energy; Sumitomo Pharmaceuticals.

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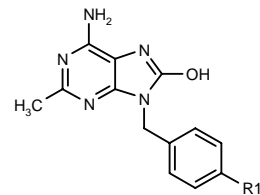
311282

6-Amino-2-butyl-9-(4-fluorobenzyl)-9H-purin-8-ol



C₁₆ H₁₈ F N₅ O; Mol wt: 315.3502

ACTION – Interferon-inducing agent, a 9-substituted adenine derivative with good oral bioavailability and high *in vivo* activity in mice, where it increased interferon levels to about 6000 IU/ml or more at doses of 3-30 mg/kg p.o. Potentially useful for the treatment of hepatitis C. Other related compounds are:



Compound	R1	Formula
311283	F	C ₁₃ H ₁₂ FN ₅ O
311284	NO ₂	C ₁₃ H ₁₂ N ₆ O ₃

SOURCES – Japan Energy; Sumitomo Pharmaceuticals.

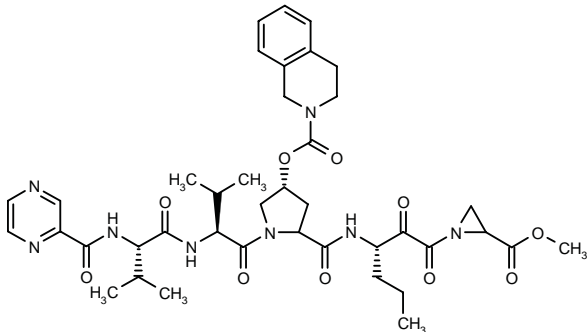
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2. Isobe, Y. et al. (Japan Energy Corp.) Type 2 helper T cell-selective immune response suppressors. EP 1043021, WO 9932122.

3. Obara, F. et al. *Synthesis and structure-activity relationship of IFN inducer, 8-hydroxyadenine - Optimization of 9-substituted groups of adenine*. 21st Symp Med Chem (Nov 28-30, Kyoto) 2001, Abst 1P-12.

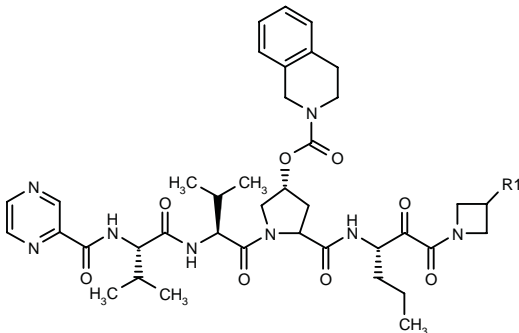
311621

1-[N-(Pyrazin-2-ylcarbonyl)-L-valyl-L-valyl-4(*R*)-(1,2,3,4-tetrahydroisoquinolin-2-ylcarbonyloxy)-DL-prolyl-L-norvalylcarbonyl]aziridine-2-carboxylic acid methyl ester



C40 H52 N8 O10; Mol wt: 804.8968

ACTION – A peptidomimetic inhibitor of serine proteases, particularly hepatitis C virus (HCV) NS3 protease ($K_i < 1 \mu\text{M}$). Other exemplified compounds are:



Compound	R1	Formula
311629	H	C ₃₉ H ₅₂ N ₈ O ₈
311631	OPh	C ₄₅ H ₅₆ N ₈ O ₉

SOURCE – Vertex.

REFERENCES

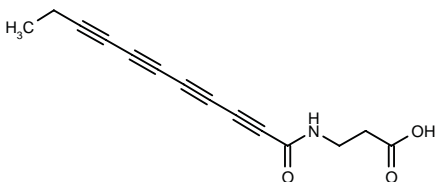
1. Perni, R. et al. (Vertex Pharmaceuticals Inc.) *Inhibitors of serine proteases, particularly hepatitis C virus NS3 protease*. WO 0174768.

F-15905

311146

N-2,4,6,8-Undecatetraynol-β-alanine

3-(2,4,6,8-Undecatetraynamido)propionic acid



C14 H11 N O3; Mol wt: 241.2449

ACTION – Antiviral agent isolated from *Mycena* sp. SANK 27299 (FERM BP-6993), potentially useful for the treatment of herpesvirus infections, particularly cytomegalovirus (CMV) infections. It displayed an IC_{50} of $33.5 \mu\text{g/ml}$ against CMV protease *in vitro*.

SOURCE – Sankyo.

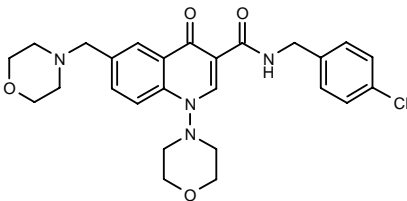
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PNU-253998

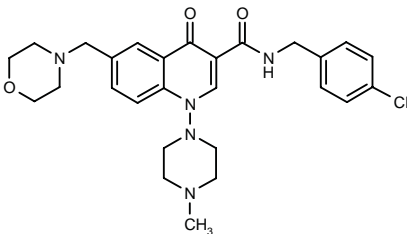
312586

N-(4-Chlorobenzyl)-1-(4-morpholinyl)-6-(morpholin-4-ylmethyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide



C26 H29 Cl N4 O4; Mol wt: 496.9921

ACTION – Non-nucleoside antiviral agent with potent and broad-spectrum activity against herpesvirus DNA polymerases including human cytomegalovirus (HCMV; $\text{IC}_{50} = 0.30 \mu\text{M}$), herpes simplex virus type 1 (HSV-1; $0.31 \mu\text{M}$) and varicella-zoster virus (VZV; $\text{IC}_{50} = 0.20 \mu\text{M}$) polymerases, with no activity against human α , γ or δ polymerases. Compound also displayed antiviral activity against HCMV ($\text{IC}_{50} = 0.6 \mu\text{M}$), HSV-1 ($\text{IC}_{50} = 8.8 \mu\text{M}$) and VZV ($\text{IC}_{50} = 0.4 \mu\text{M}$). Furthermore, good oral bioavailability has been reported in animals (84% in dogs; 66% in rats). Another related compound is:



PNU-276484 [312587]: C27 H32 Cl N5 O3

SOURCE – Pharmacia.

REFERENCES

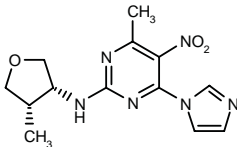
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2. Schnute, M.E. et al. *1-Amino-4-oxo-1,4-dihydroquinolines with broad-spectrum antitherpetic activity*. 41st Intersci Conf Antimicrob Agents Chemother (Dec 16-19, Chicago) 2001, Abst F-1669.

T-0902395

312704

4-(1*H*-Imidazol-1-yl)-6-methyl-*N*-[4(*S*)-methyltetrahydrofuran-3(*R*)-yl]-5-nitropyrimidin-2-amine



C13 H16 N6 O3; Mol wt: 304.3084

ACTION – Selective non-nucleoside human cytomegalovirus (HCMV) UL70 primase inhibitor (IC₅₀ = 0.15 μM for inhibition of viral DNA replication) shown to block HCMV infection with IC₅₀ values of 0.13-0.4 μM in a cell-based HCMV assay. Compound exhibited good water solubility and *in vitro* metabolic stability, as well as a favorable pharmacokinetic profile, with an oral bioavailability of 57%.

SOURCE – Tularik.

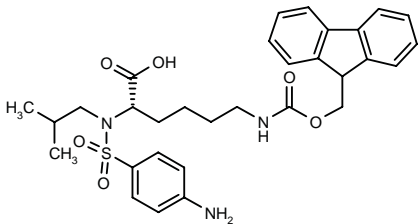
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AIDS MEDICINES

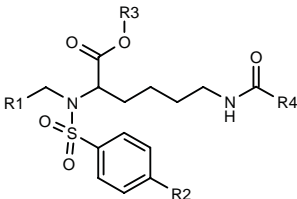
310382

2(*S*)-[*N*-(4-Aminophenylsulfonyl)-*N*-isobutylamino]-6-(9*H*-fluoren-9-ylmethoxycarbonylamino)hexanoic acid



C31 H37 N3 O6 S; Mol wt: 579.7143

ACTION – HIV aspartyl protease inhibitor (K_i = 2.1 nM) with antiviral activity against HIV-1 and HIV-2. Other exemplified amino acid derivatives include the following:



Compound	R1	R2	R3	R4	Isomer	Formula
310383	i-Pr	Me	H	9-fluorenyl-CH2O		C ₃₂ H ₃₈ N ₂ O ₆ S
310384	cyclopropyl	Me	H	9-fluorenyl-CH2O		C ₃₂ H ₃₈ N ₂ O ₆ S
310385	i-Pr	Me	H	9-fluorenyl-CH2O	S	C ₃₂ H ₃₈ N ₂ O ₆ S
310386	i-Pr	Me	Na	9-fluorenyl-CH2O	S	C ₃₂ H ₃₇ N ₂ NaO ₆ S
310387	i-Pr	Me	H	3-indolyl-CH2CH2	S	C ₂₈ H ₃₇ N ₃ O ₅ S
310388	i-Pr	Me	H	CH2CH2Ph	S	C ₂₆ H ₃₆ N ₂ O ₅ S
310389	i-Pr	NH2	H	2,3-(MeO)2-Ph-CH2CH2	S	C ₂₇ H ₃₉ N ₃ O ₇ S
310390	i-Pr	NH2	H	CH2OPh	S	C ₂₄ H ₃₃ N ₃ O ₆ S

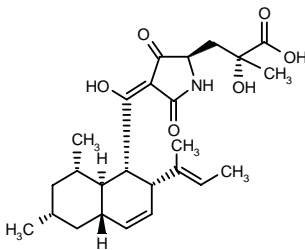
SOURCE – Pharmacor.

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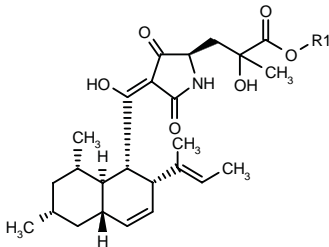
311566

3-[4-[1-[(1*S*,2*R*,4*aS*,6*R*,8*S*,8*aR*)-6,8-Dimethyl-2-(1-methyl-1-propenyl)-1,2,4*a*,5,6,7,8,8*a*-octahydronaphthalen-1-yl]-1-hydroxymethylene]-3,5-dioxopyrrolidin-2(*R*)-yl]-2(*R*)-hydroxy-2-methylpropionic acid



C25 H35 N O6; Mol wt: 445.5525

ACTION – Agent with chemokine CCR5-antagonist activity isolated from cultures of the microorganism *Chaetomium globosum* Kunze SCH 1705 (ATCC 74489). It displayed an IC₅₀ of 78.6 nM against CCR5 receptors in membrane preparations from NIH/3T3 cells. Potentially useful for the treatment of HIV infection. Other compounds from the same source are:



Compound	R1	Isomer	Formula
311567	H	S	C ₂₅ H ₃₅ NO ₆
311571	Me	R	C ₂₆ H ₃₇ NO ₆

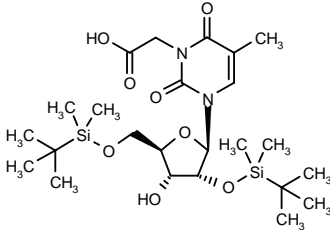
SOURCE – Schering-Plough.

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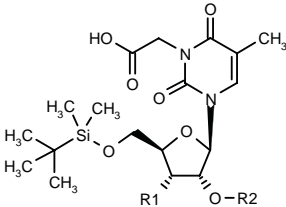
311769

2-[3-[2,5-Bis-*O*-[*tert*-butyl(dimethyl)silyl]-β-D-ribofuran-
osyl]thymine-3-yl]acetic acid



C24 H44 N2 O8 Si2; Mol wt: 544.7896

ACTION – Anti-HIV agent, a non-nucleoside reverse transcriptase (RT) inhibitor (IC₅₀ = 138 and 158 μM against wild-type and Glu138Lys mutant RT, respectively) shown to inhibit HIV-1-induced cytopathicity in CEM cells (EC₅₀ = 4.5 μM), as well as the replication of HIV-1/138Lys (EC₅₀ = 2 μM). Other related compounds are:



Compound	R1	R2	Formula
311771	t-BuSi(Me)2O	H	C ₂₄ H ₄₄ N ₂ O ₈ Si ₂
311772	H	t-BuSi(Me)2	C ₂₄ H ₄₄ N ₂ O ₇ Si ₂

SOURCES – CSIC, Madrid (ES); Rega Institute for Medical Research, Leuven (BE).

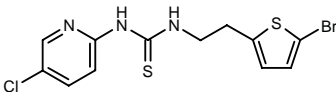
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DDE-934

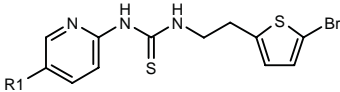
310715

N-[2-(5-Bromothiophen-2-yl)ethyl]-*N'*-(5-chloropyridin-2-yl)thiourea



C12 H11 Br Cl N3 S2; Mol wt: 376.7289

ACTION – Anti-HIV agent, an inhibitor of HIV reverse transcriptase (IC₅₀ = 0.10 μM) with an IC₅₀ of 12 nM for inhibition of HIV replication in human peripheral blood mononuclear cells. Other 5-bromothiophenethyl thioureas include the following:



Compound	R1	Formula
DDE-933 [310713]	Me	C ₁₃ H ₁₄ BrN ₃ S ₂
DDE-935 [310714]	H	C ₁₂ H ₁₂ BrN ₃ S ₂
DDE-946 [310716]	Br	C ₁₂ H ₁₁ Br ₂ N ₃ S ₂

SOURCE – Parker Hughes Institute, Roseville, MN (US).

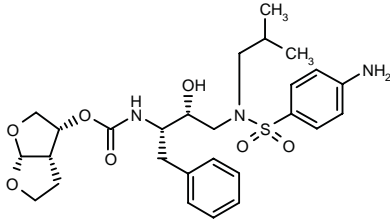
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1. Venkatachalam, T.K. et al. *Regiospecific synthesis, X-ray crystal structure and biological activities of 5-bromothiophenethyl thioureas*. Tetrahedron Lett 2001, 42(38): 6629.

TMC-114

310828

N-[3-[*N*-(4-Aminophenylsulfonyl)-*N*-isobutylamino]-1(*S*)-benzyl-2(*R*)-hydroxypropyl]carbamic acid (3*R*,3*aS*,6*aR*)-perhydrofuro[2,3-*b*]furan-3-yl ester



C27 H37 N3 O7 S; Mol wt: 547.6693

ACTION – Anti-HIV agent, a bisfuransulfonamide HIV protease inhibitor (K_i = 2.1 nM) with excellent activity against wild-type HIV-1 (EC₅₀ and EC₉₀ = 4.7 and 10.3 nM, respectively), as well as against protease inhibitor-resistant HIV variants (EC₅₀ < 100 nM). Compound was relatively stable in the presence of human liver microsomes and exhibited high plasma levels (7490 ng/ml) following oral administration at 20 mg/kg to dogs. In a phase I trial in healthy volunteers, compound was administered as single oral doses of 100-4000 mg; the elimination half-life was dose-independent and averaged 10 h, and plasma levels at 8-12 h after dosing at 800 mg or above exceeded the protein-adjusted IC₅₀ values for protease inhibitor-resistant isolates. Compound was well tolerated, the only adverse events being transient localized paresthesias in half of the subjects given 3200 mg.

SOURCE – Tibotec-Virco.

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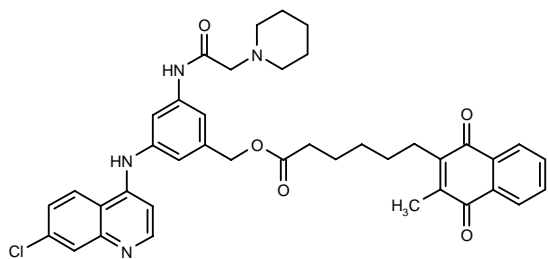
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TREATMENT OF PROTOZOAL DISEASES

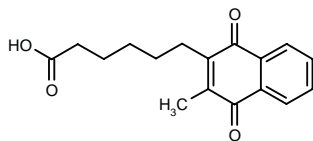
311369

6-(3-Methyl-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-hexanoic acid 3-(7-chloroquinolin-4-ylamino)-5-[2-(1-piperidiny)acetamido]benzyl ester



C40 H41 Cl N4 O5; Mol wt: 693.2399

ACTION – Antimalarial agent, a prodrug form of a *Plasmodium falciparum* glutathione reductase inhibitor (**312582**; IC₅₀ = 0.5 μM) conjugated with quinoline-based alcohol, active *in vitro* against chloroquine-sensitive and -resistant strains of *P. falciparum* (EC₅₀ = 23.1-36.5 nM). In *Plasmodium berghei*-infected mice, compound at a dose of 40 mg/kg/day i.p. for 4 days produced a significant increase in survival time (from 8 to 24 days) and a decrease of more than 99.9% in parasitemia.



312582: C17 H18 O4

SOURCE – Tibotec-Virco.

REFERENCES

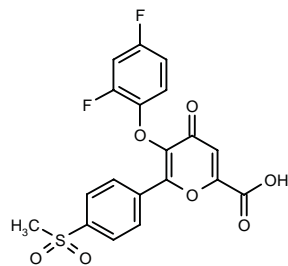
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TREATMENT OF MUSCULOSKELETAL AND CONNECTIVE TISSUE DISEASES

ANTIARTHRITIC DRUGS

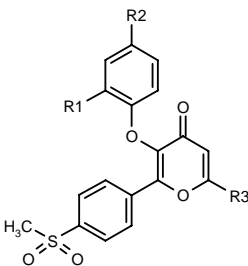
310473

5-(2,4-Difluorophenoxy)-6-[4-(methylsulfonyl)phenyl]-4-oxo-4H-pyran-2-carboxylic acid



C19 H12 F2 O7 S; Mol wt: 422.3588

ACTION – Selective cyclooxygenase type 2 (COX-2) inhibitor (IC₅₀ = 0.42 μM in human whole blood) with > 1,000-fold selectivity over COX-1. Potentially useful for the treatment of pain, fever, inflammation, colorectal cancer and neurodegenerative diseases, as well as for inhibiting prostanoid-induced smooth muscle contraction. Other exemplified 4-sulfonylphenyl-substituted pyranones include the following:



Compound	R1	R2	R3	Formula
310474	Me	F	Me	C ₂₀ H ₁₇ FO ₅ S
310475	F	Br	Me	C ₁₉ H ₁₄ BrFO ₅ S
310476	Me	H	Me	C ₂₀ H ₁₈ O ₅ S
310477	F	F	CH2OH	C ₁₉ H ₁₄ F ₂ O ₆ S
310478	H	F	CH2OMe	C ₂₀ H ₁₇ FO ₆ S
310479	H	F	CH2OAc	C ₂₁ H ₁₇ FO ₇ S
310480	H	Me	CHF2	C ₂₀ H ₁₆ F ₂ O ₅ S

SOURCE – Almirall Prodesfarma.

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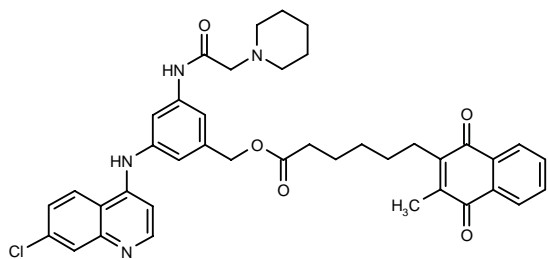
4. Pauwels, R. *The development on the next generation of antiretrovirals with activity against drug-resistance strains of HIV-1*. 8th Eur Conf Clin Aspects Treat HIV Infect (Oct 28-31, Athens) 2001, Abst O32.

5. Van Der Geest, R. et al. *Safety, tolerability and pharmacokinetics of escalating single oral doses of TMC114, a novel protease inhibitor (PI) highly active against HIV-1 variants resistant to other PIs*. 41st Intersci Conf Antimicrob Agents Chemother (Dec 16-19, Chicago) 2001, Abst I-1934.

TREATMENT OF PROTOZOAL DISEASES

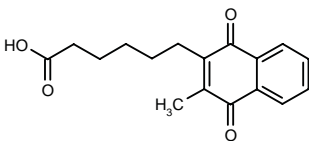
311369

6-(3-Methyl-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-hexanoic acid 3-(7-chloroquinolin-4-ylamino)-5-[2-(1-piperidiny)acetamido]benzyl ester



C40 H41 Cl N4 O5; Mol wt: 693.2399

ACTION – Antimalarial agent, a prodrug form of a *Plasmodium falciparum* glutathione reductase inhibitor (**312582**; IC₅₀ = 0.5 µM) conjugated with quinoline-based alcohol, active *in vitro* against chloroquine-sensitive and -resistant strains of *P. falciparum* (EC₅₀ = 23.1-36.5 nM). In *Plasmodium berghei*-infected mice, compound at a dose of 40 mg/kg/day i.p. for 4 days produced a significant increase in survival time (from 8 to 24 days) and a decrease of more than 99.9% in parasitemia.



312582: C17 H18 O4

SOURCE – Tibotec-Virco.

REFERENCES

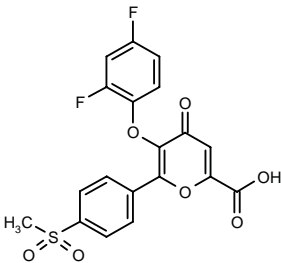
1. Davioud-Chervet, E. et al. *A prodrug from of a Plasmodium falciparum glutathione reductase inhibitor conjugated with a 4-anilinoquinoline*. J Med Chem 2001, 44(24): 4268.

TREATMENT OF MUSCULOSKELETAL AND CONNECTIVE TISSUE DISEASES

ANTIARTHRITIC DRUGS

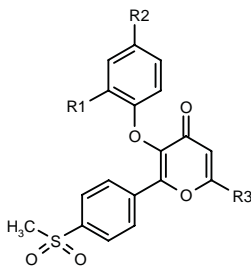
310473

5-(2,4-Difluorophenoxy)-6-[4-(methylsulfonyl)phenyl]-4-oxo-4H-pyran-2-carboxylic acid



C19 H12 F2 O7 S; Mol wt: 422.3588

ACTION – Selective cyclooxygenase type 2 (COX-2) inhibitor (IC₅₀ = 0.42 µM in human whole blood) with > 1,000-fold selectivity over COX-1. Potentially useful for the treatment of pain, fever, inflammation, colorectal cancer and neurodegenerative diseases, as well as for inhibiting prostanoid-induced smooth muscle contraction. Other exemplified 4-sulfonylphenyl-substituted pyranones include the following:



Compound	R1	R2	R3	Formula
310474	Me	F	Me	C ₂₀ H ₁₇ FO ₅ S
310475	F	Br	Me	C ₁₉ H ₁₄ BrFO ₅ S
310476	Me	H	Me	C ₂₀ H ₁₈ O ₅ S
310477	F	F	CH ₂ OH	C ₁₉ H ₁₄ F ₂ O ₆ S
310478	H	F	CH ₂ OMe	C ₂₀ H ₁₇ FO ₆ S
310479	H	F	CH ₂ OAc	C ₂₁ H ₁₇ FO ₇ S
310480	H	Me	CHF ₂	C ₂₀ H ₁₆ F ₂ O ₅ S

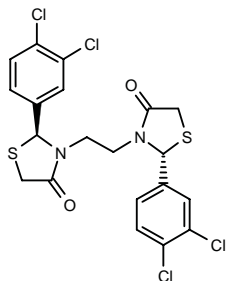
SOURCE – Almirall Prodesfarma.

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1. Crespo Crespo, M.I. et al. (Almirall Prodesfarma, SA) *2-Phenylpyran-4-one derivs*. WO 0168633.

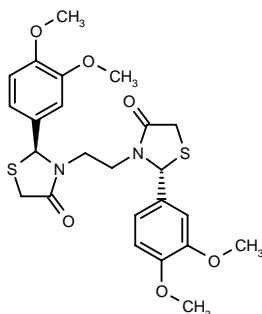
310481

(2*R**,2'*S*'*)-3,3'-(1,2-Ethanediy)bis[2-(3,4-dichlorophenyl)thiazolidin-4-one]



C20 H16 Cl4 N2 O2 S2; Mol wt: 522.3024

ACTION – Antiinflammatory agent, a bithiazolidinone with antiinflammatory (carrageenan-induced paw edema) and analgesic (acetic acid-induced writhing, hot-plate test) activity in rats (50 mg/kg p.o.) superior to phenylbutazone at the same dose and equal to indomethacin (5 mg/kg), but with extremely low gastric toxicity. Another related compound is:



310483: C24 H28 N2 O6 S2

SOURCE – Università degli Studi di Messina, Messina (IT).

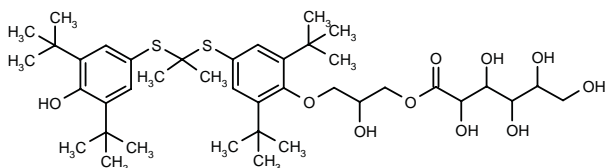
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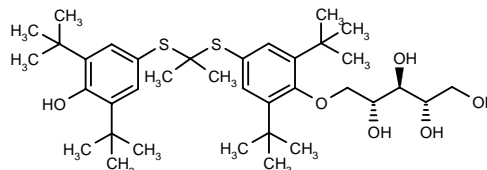
310646

2,3,4,5,6-Pentahydroxyhexanoic acid 3-[2,6-di-*tert*-butyl-4-[1-(3,5-di-*tert*-butyl-4-hydroxyphenyl)sulfanyl]-1-methylethylsulfanyl]phenoxy]-2-hydroxypropyl ester



C40 H64 O10 S2; Mol wt: 769.0676

ACTION – Agent with the ability to inhibit the expression of vascular cell adhesion molecule-1 (VCAM-1), as demonstrated by inhibition of TNF- α -induced expression of VCAM-1 in human aortic endothelial cells with an IC₅₀ of 7.0 μ M. Potentially useful for the treatment of inflammatory disorders, particularly rheumatoid arthritis, osteoarthritis, asthma, dermatitis, psoriasis, transplant rejection, autoimmune diabetes and multiple sclerosis. Further applications include cardiovascular disorders such as atherosclerosis, postangioplasty restenosis, coronary and small artery disease, angina, diabetes and diabetic nephropathy and retinopathy, as well as hypercholesterolemia and hyperlipidemia. Another exemplified compound is:



310647: C36 H58 O6 S2

SOURCE – AtheroGenics.

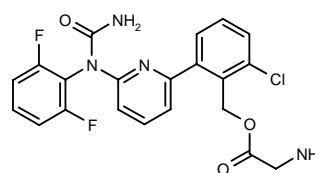
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1. Meng, C.Q. et al. (AtheroGenics, Inc.) *Thioketals and thioethers for inhibiting the expression of VCAM-1*. WO 0170757.

310821

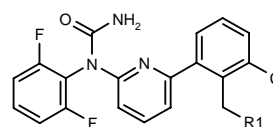
2-Aminoacetic acid 2-chloro-6-[6-[1-(2,6-difluorophenyl)ureido]pyridin-2-yl]benzyl ester

Glycine 2-chloro-6-[6-[1-(2,6-difluorophenyl)ureido]pyridin-2-yl]benzyl ester



C21 H17 Cl F2 N4 O3; Mol wt: 446.8393

ACTION – An inhibitor of p38 mitogen-activated protein (MAP) kinase, expected to be useful for the treatment of inflammatory and autoimmune diseases, destructive bone disorders, proliferative disorders, infectious diseases, neurodegenerative diseases, allergies, stroke-related reperfusion and ischemia, angiogenic disorders, thrombin-induced platelet aggregation and conditions associated with prostaglandin endoperoxide synthase-2 such as edema, fever and pain. Other specifically claimed pyridine-containing compounds are:



Compound	R1	Formula
310822	i-PrCH(NH ₂)COO	C ₂₄ H ₂₃ ClF ₂ N ₄ O ₃
310824	CONH ₂	C ₂₀ H ₁₅ ClF ₂ N ₄ O ₃
310825	NHCH ₂ CO ₂ Et	C ₂₃ H ₂₁ ClF ₂ N ₄ O ₃

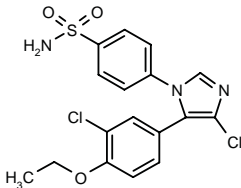
SOURCE – Vertex.

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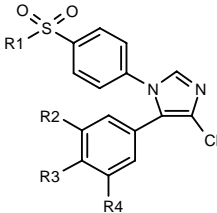
310890

4-[4-Chloro-5-(3-chloro-4-ethoxyphenyl)-1*H*-imidazol-1-yl]benzenesulfonamide



C17 H15 Cl2 N3 O3 S; Mol wt: 412.2955

ACTION – A selective cyclooxygenase type 2 (COX-2) inhibitor displaying 97% inhibition at 0.1 μM, while having no activity against COX-1. Potentially useful for the treatment of inflammation, pain, fever, prostanoid-induced smooth muscle contraction, dysmenorrhea, familial adenomatous polyposis, colon cancer, stroke, epilepsy and dementia, e.g., Alzheimer's disease. Other specifically claimed 4-chloroimidazole derivatives are:



Compound	R1	R2	R3	R4	Formula
310892	Me	H	i-PrO	H	C ₁₉ H ₁₉ ClN ₂ O ₃ S
310894	Me	OMe	F	H	C ₁₇ H ₁₄ ClFN ₂ O ₃ S
310895	Me	F	OEt	H	C ₁₈ H ₁₆ ClFN ₂ O ₃ S
310897	Me	F	H	F	C ₁₆ H ₁₁ ClF ₂ N ₂ O ₂ S
310898	Me	Cl	OMe	H	C ₁₇ H ₁₄ Cl ₂ N ₂ O ₃ S
310900	Me	Cl	OEt	H	C ₁₈ H ₁₆ Cl ₂ N ₂ O ₃ S
310901	Me	-OCH2O-		H	C ₁₇ H ₁₃ ClN ₂ O ₄ S
310903	Me	Cl	OMe	Cl	C ₁₇ H ₁₃ Cl ₃ N ₂ O ₃ S
310905	Me	H	i-Pr	H	C ₁₉ H ₁₉ ClN ₂ O ₂ S
310906	Me	H	N(Et)2	H	C ₂₀ H ₂₂ ClN ₃ O ₂ S
310908	NH2	OMe	F	H	C ₁₆ H ₁₃ ClFN ₃ O ₃ S
310910	NH2	F	OEt	H	C ₁₇ H ₁₅ ClFN ₃ O ₃ S
310912	NH2	Cl	OMe	H	C ₁₆ H ₁₃ Cl ₂ N ₃ O ₃ S
310913	NH2	Cl	OMe	Cl	C ₁₆ H ₁₂ Cl ₃ N ₃ O ₃ S
310914	Me	H	Pr	H	C ₁₉ H ₁₉ ClN ₂ O ₂ S

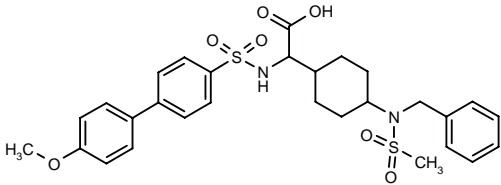
SOURCE – Uriach.

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310933

2-[4-[*N*-Benzyl-*N*-(methylsulfonyl)amino]cyclohexyl]-2-(4'-methoxybiphenyl-4-ylsulfonamido)acetic acid



C29 H34 N2 O7 S2; Mol wt: 586.7266

ACTION – Matrix metalloproteinase inhibitor, potentially useful in the treatment of rheumatoid arthritis, osteoarthritis and cancer.

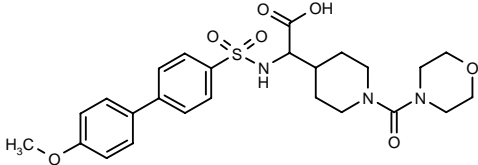
SOURCE – Procter & Gamble.

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1. Natchus, M.G. et al. (The Procter & Gamble Co.) *Carbocyclic side chain containing metalloprotease inhibitors*. WO 0170682.

310934

2-(4'-Methoxybiphenyl-4-ylsulfonamido)-2-[1-(morpholin-4-ylcarbonyl)piperidin-4-yl]acetic acid



C25 H31 N3 O7 S; Mol wt: 517.5999

ACTION – Matrix metalloproteinase inhibitor, potentially useful in the treatment of rheumatoid arthritis, osteoarthritis and cancer.

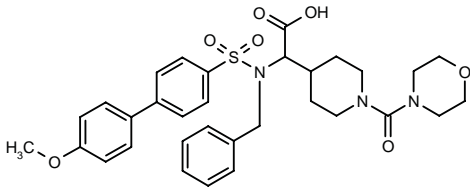
SOURCE – Procter & Gamble.

REFERENCES

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310935

2-[*N*-Benzyl-*N*-(4'-methoxybiphenyl-4-ylsulfonyl)amino]-2-[1-(morpholin-4-ylcarbonyl)piperidin-4-yl]acetic acid



C32 H37 N3 O7 S; Mol wt: 607.7243

ACTION – Matrix metalloproteinase inhibitor, potentially useful in the treatment of rheumatoid arthritis, osteoarthritis and cancer.

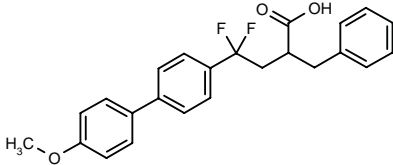
SOURCE – Procter & Gamble.

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310936

2-Benzyl-4,4-difluoro-4-(4'-methoxybiphenyl-4-yl)butyric acid



C24 H22 F2 O3; Mol wt: 396.4308

ACTION – Matrix metalloproteinase inhibitor, potentially useful in the treatment of rheumatoid arthritis, osteoarthritis and cancer.

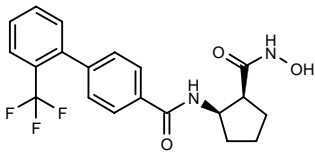
SOURCE – Procter & Gamble.

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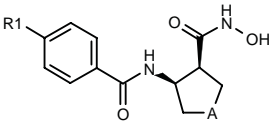
311024

(1*S*,2*R*)-2-[2'-(Trifluoromethyl)biphenyl-4-ylcarboxamido]-cyclopentanecarbohydroxamic acid

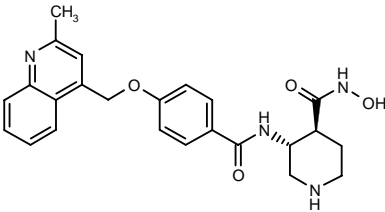


C20 H19 F3 N2 O3; Mol wt: 392.3751

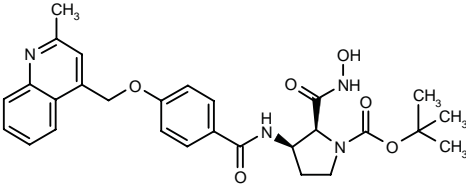
ACTION – An inhibitor of matrix metalloproteinases (MMPs), TNF-α and aggrecanase, potentially useful for the treatment of inflammatory diseases and for the prevention of cartilage degradation. Other specifically claimed cyclic β-amino acid derivatives include the following:



Compound	R1	A	Formula
311025	2-Me-4-quinolyl-CH2O	-N(ethynyl-CH2)-	C26H26N4O4
311027	2-Me-4-quinolyl-CH2O	-CO-	C24H23N3O5
311028	2-Me-4-quinolyl-CH2O	-NH-	C23H24N4O4
311030	2-Me-4-quinolyl-CH2O	-N(cyclopentyl)CH2-	C29H34N4O4
311031	2-Me-4-quinolyl-CH2O	-N(4-morpholinyl-COCH2)CH2-	C30H35N5O6
311032	2-Me-4-quinolyl-CH2O	-N[vinyl-C(Me)2]CH2-	C29H34N4O4
311033	3-Ph-4,5-dihydro-5-isoxazolyl	-CH2-	C22H23N3O4



311029: C24 H26 N4 O4



311034: C28 H32 N4 O6

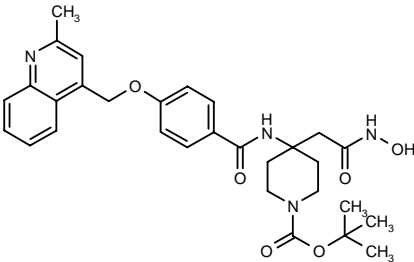
SOURCE – Bristol-Myers Squibb.

REFERENCES

1. Duan, J. et al. (DuPont Pharmaceuticals Co.) *Cyclic β-amino acid derivs. as inhibitors of matrix metalloproteases and TNF-alpha*. WO 0170673.

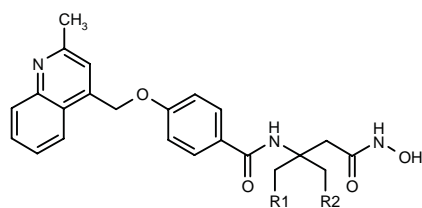
311035

2-[1-(*tert*-Butoxycarbonyl)-4-[4-(2-methylquinolin-4-ylmethoxy)benzamido]piperidin-4-yl]acetohydroxamic acid



C30 H36 N4 O6; Mol wt: 548.6364

ACTION – An inhibitor of matrix metalloproteinases (MMPs), TNF-α and aggrecanase, potentially useful for the treatment of inflammatory diseases and for the prevention of cartilage degradation. Other specifically claimed β-amino acid derivatives include the following:



Compound	R1,R2	Formula
311036	-CH2N(t-BuOCONHCH2CH2)CH2-	C ₃₂ H ₄₁ N ₅ O ₆
311037	-CH2N(4-imidazolyl-CH2)CH2-	C ₂₉ H ₃₂ N ₆ O ₄
311038	-CH2N[C(=NH)NH2]CH2-	C ₂₆ H ₃₀ N ₆ O ₄
311039	-NH(CH2)2-	C ₂₅ H ₂₈ N ₄ O ₄
311041	-N(3-Pyr-CH2)CH2-	C ₃₀ H ₃₁ N ₅ O ₄
311042	-SCH(Me)-	C ₂₅ H ₂₇ N ₃ O ₄ S
311044	-CH2C(=CH2)CH2-	C ₂₇ H ₂₉ N ₃ O ₄
311045	-CH2CH(2-thienyl-CONH)CH2-	C ₃₁ H ₃₂ N ₄ O ₅ S
311046	-(CH2)3N(Ac)-	C ₂₈ H ₃₂ N ₄ O ₅

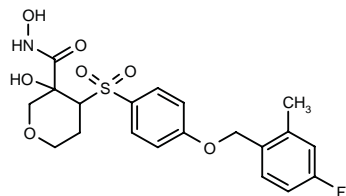
SOURCE – Bristol-Myers Squibb.

REFERENCES

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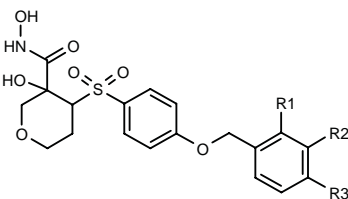
311130

4-[4-(4-Fluoro-2-methylbenzyloxy)phenylsulfonyl]-3-hydroxytetrahydropyran-3-carbohydroxamic acid



C20 H22 F N O7 S; Mol wt: 439.4578

ACTION – An inhibitor of matrix metalloproteinases (MMPs), especially MMP-13 (collagenase 3) and aggrecanase. Potentially useful for the treatment of arthritis, inflammatory bowel disease, Crohn’s disease, emphysema, acute respiratory distress syndrome, asthma, chronic obstructive pulmonary disease, Alzheimer’s disease, transplant rejection, cachexia, allergy, cancer, tissue ulceration, restenosis, osteoporosis, stroke, pain and heart failure, among a wide variety of MMP-mediated diseases. Other specifically claimed sulfonyl hydroxamic acids are:



Compound	R1	R2	R3	Formula
311131	H	Cl	H	C ₁₉ H ₂₀ ClNO ₇ S
311134	H	H	Cl	C ₁₉ H ₂₀ ClNO ₇ S
311137	Cl	H	H	C ₁₉ H ₂₀ ClNO ₇ S
311139	H	F	H	C ₁₉ H ₂₀ FNO ₇ S
311142	Me	H	H	C ₂₀ H ₂₃ NO ₇ S
311144	Me	H	F	C ₂₀ H ₂₂ FNO ₇ S

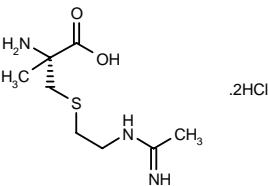
SOURCE – Pfizer.

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1. Noe, M.C. (Pfizer Products Inc.) *Gem substd. sulfonyl hydroxamic acids as MMP inhibitors*. EP 1138680, JP 2001316383.

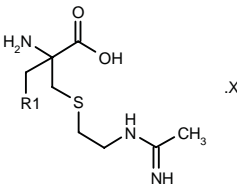
311198

S-[2-(1-Iminoethylamino)ethyl]-2-methyl-L-cysteine dihydrochloride



C8 H17 N3 O2 S . 2HCl; Mol wt: 292.2291

ACTION – Nitric oxide synthase (NOS) inhibitor with IC₅₀ values of 3.1, 77 and 15 μM, respectively, against human inducible NOS (iNOS), endothelial NOS (eNOS) and neuronal NOS (nNOS). In addition, compound inhibited the production of NO in human cartilage with an IC₅₀ of 0.7 μM. Potentially useful for the treatment of inflammatory disorders including arthritis, asthma, bronchitis, preterm labor, psoriasis, dermatitis, pancreatitis, hepatitis, inflammatory bowel disease, Crohn’s disease, cancer, etc. Other exemplified amidino compounds are:



Compound	R1	Isomer	X	Formula
311199	OMe	L	2HCl	C ₉ H ₁₉ N ₃ O ₃ S.2ClH
311200	H	DL	2CF3CO2H	C ₈ H ₁₇ N ₃ O ₂ S.2C ₂ HF ₃ O ₂

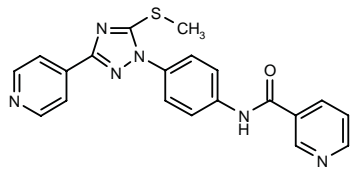
SOURCE – Pharmacia.

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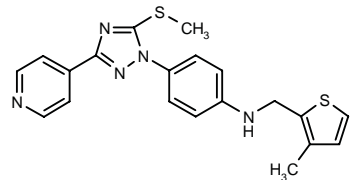
311206

N-[4-[5-(Methylsulfanyl)-3-(4-pyridyl)-1*H*-1,2,4-triazol-1-yl]phenyl]pyridine-3-carboxamide



C20 H16 N6 O S; Mol wt: 388.4534

ACTION – IL-2 production inhibitor (IC₅₀ = 10 μM), potentially useful for the treatment of autoimmune diseases, inflammation, immune disorders, transplant rejection and other disorders associated with IL-2-mediated immune responses. Another exemplified phenyl-substituted 1,2,4-triazole is:



311207: C20 H19 N5 S2

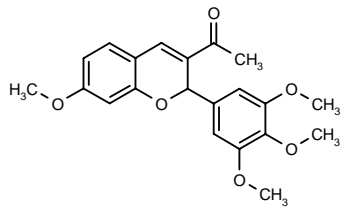
SOURCE – Boehringer Ingelheim.

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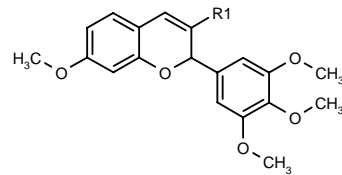
311311

1-[7-Methoxy-2-(3,4,5-trimethoxyphenyl)-2*H*-1-benzopyran-3-yl]ethanone



C21 H22 O6; Mol wt: 370.3988

ACTION – An inhibitor of TNF-α production, as demonstrated in lipopolysaccharide-stimulated human peripheral blood mononuclear cells (PBMCs; IC₅₀ = 0.1 μM). Potentially useful for the treatment of inflammatory and immune disorders, bone resorptive diseases, pulmonary diseases and autoimmune diseases. Other exemplified benzopyran derivatives are:



Compound	R1	Formula
311312	CONH2	C ₂₀ H ₂₁ NO ₆
311313	CHO	C ₂₀ H ₂₀ O ₆
311314	CN	C ₂₀ H ₁₉ NO ₅

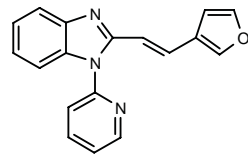
SOURCE – Chugai.

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1. Cheng, J.F. et al. (Chugai Pharmaceutical Co. Ltd.) *Benzopyranes useful as TNF α inhibitors*. WO 0172735.

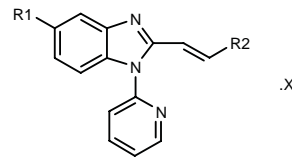
311414

2-[(*E*)-2-(3-Furyl)vinyl]-1-(2-pyridyl)-1*H*-benzimidazole



C18 H13 N3 O; Mol wt: 287.3207

ACTION – A cyclooxygenase type 2 (COX-2) inhibitor, expected to be useful as an antiinflammatory and analgesic agent. Other specifically claimed benzimidazole derivatives include the following:



Compound	R1	R2	X	Formula
311416	H	2-thienyl		C ₁₈ H ₁₃ N ₃ S
311417	Me	3-furyl	oxalate	C ₁₉ H ₁₅ N ₃ O ₂ ·C ₂ H ₂ O ₄
311419	OMe	3-furyl	oxalate	C ₁₉ H ₁₅ N ₃ O ₂ ·C ₂ H ₂ O ₄

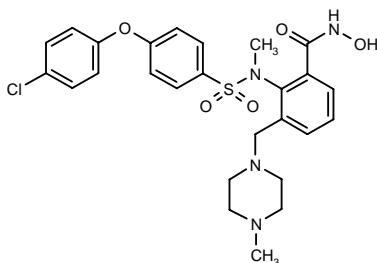
SOURCE – Pfizer.

REFERENCES

1. Okumura, Y. et al. (Pfizer Inc.) *Benzimidazole cyclooxygenase-2 inhibitors*. US 6310079.

311498

2-[N-[4-(4-Chlorophenoxy)phenylsulfonyl]-N-methyl-amino]-3-(4-methylpiperazin-1-ylmethyl)benzohydroxamic acid



C26 H29 Cl N4 O5 S; Mol wt: 545.0571

ACTION – Matrix metalloproteinase (MMP) inhibitor active against gelatinase B (MMP-9; IC_{50} = 1 nM) and collagenase 3 (MMP-13; IC_{50} = 0.8 nM), with good selectivity over interstitial collagenase (MMP-1; IC_{50} = 155 nM). Compared with the reference compound CGS-27023A, it was about 10-fold more potent *in vitro* against MMP-9 and MMP-13 and was at least equipotent in a bovine cartilage explant assay. *In vivo*, in a rat sponge-wrapped cartilage model, oral doses of 50 mg/kg b.i.d. produced 75% inhibition of collagen degradation, compared to 55% inhibition with CGS-27023A at the same dose. Potentially useful for the treatment of cartilage degradation in osteoarthritis.

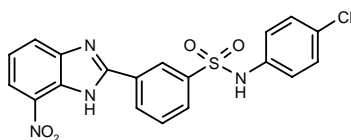
SOURCES – Immunex; Wyeth-Ayerst.

REFERENCES

1. Levin, J.I. et al. *The discovery of anthranilic acid-based MMP inhibitors: Part 3: Incorporation of basic amines*. Bioorg Med Chem Lett 2001, 11(22): 2975.

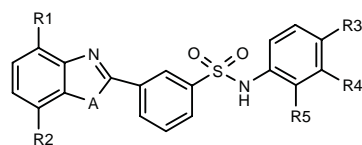
311554

N-(4-Chlorophenyl)-3-(7-nitro-1H-benzimidazol-2-yl)benzenesulfonamide



C19 H13 Cl N4 O4 S; Mol wt: 428.8547

ACTION – Phosphodiesterase type 7 (PDE7) inhibitor, potentially useful for the treatment of autoimmune diseases including rheumatoid arthritis, multiple sclerosis and systemic lupus erythematosus, transplant rejection, psoriasis, restenosis following angioplasty and atherosclerosis, osteoporosis, asthma, inflammatory bowel disease, pancreatitis, chronic obstructive pulmonary disease, chronic bronchitis, atopic dermatitis and allergic rhinitis. Other specifically claimed biarylsulfonamides include the following:



Compound	R1	R2	R3	R4	R5	A	Formula
311555	H	NO2	H	CN	H	NH	C ₂₀ H ₁₃ N ₅ O ₄ S
311556	H	NO2	Br	H	Cl	NH	C ₁₉ H ₁₂ BrClN ₄ O ₄ S
311557	H	NO2	Cl	H	Me	NH	C ₂₀ H ₁₅ ClN ₄ O ₄ S
311559	H	CO2H	Cl	H	Me	NH	C ₂₁ H ₁₆ ClN ₃ O ₄ S
311560	H	CO2H	H	H	Cl	NH	C ₂₀ H ₁₄ ClN ₃ O ₄ S
311561	CO2H	H	Cl	H	Me	O	C ₂₁ H ₁₅ ClN ₂ O ₅ S
311562	NO2	H	CN	H	H	O	C ₂₀ H ₁₂ N ₄ O ₅ S

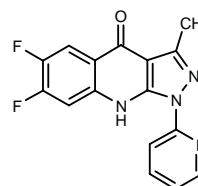
SOURCE – Darwin Discovery.

REFERENCES

1. Lowe, C. et al. (Darwin Discovery Ltd.) *Heterobiarylsulphonamides and their use as PDE 7 inhibitors*. WO 0174786.

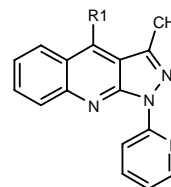
311613

6,7-Difluoro-3-methyl-1-(2-pyridyl)-4,9-dihydro-1H-pyrazolo[3,4-b]quinolin-4-one

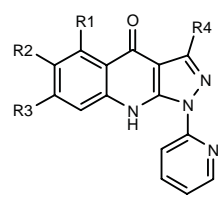


C16 H10 F2 N4 O; Mol wt: 312.2780

ACTION – Cyclooxygenase (COX) inhibitor with IC_{50} values of 0.527 and 0.295 μ M, respectively, against COX-1 and COX-2 expressed in Sf-21 cells. Compound demonstrated antiinflammatory activity in the carrageenan-induced edema model in rats after p.o. administration (10 mg/kg). It also showed analgesic activity in the acetic acid-induced writhing test in mice (10 mg/kg p.o.), antipyretic activity in the yeast-induced fever model in rats (10 mg/kg p.o.) and antiarthritic activity in an adjuvant-induced arthritis model in rats (10 mg/kg/day p.o. for 14 days). Potentially useful for the treatment of immune diseases, transplant rejection, allergies, inflammation and rheumatoid arthritis. Other exemplified condensed pyrazole derivatives are:



Compound	R1	Formula
311614	NHPr	C ₁₉ H ₁₉ N ₅
311615	OPr	C ₁₉ H ₁₈ N ₄ O
311616	cyclopentyl-O	C ₂₁ H ₂₀ N ₄ O



Compound	R1	R2	R3	R4	Formula
311617	CO2Me	H	H	Me	C ₁₈ H ₁₄ N ₄ O ₃
311623	H	Cl	F	Me	C ₁₆ H ₁₀ ClFN ₄ O
311624	H	Cl	H	H	C ₁₅ H ₉ ClN ₄ O
311625	F	H	H	Me	C ₁₆ H ₁₁ FN ₄ O
311626	H	H	H	H	C ₁₅ H ₁₀ N ₄ O

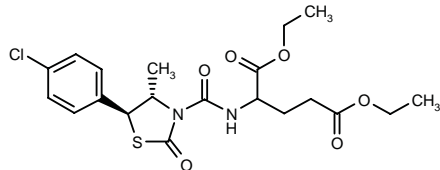
SOURCE – Takeda.

REFERENCES

1. Uchikawa, O. et al. (Takeda Chemical Industries, Ltd.) *Condensed pyrazole derivs., process for producing the same and use thereof.* JP 2001342188, WO 0172749.

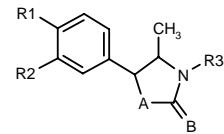
311627

trans-2-[5-(4-Chlorophenyl)-4-methyl-2-oxothiazolidin-3-ylcarboxamido]glutaric acid diethyl diester



C20 H25 Cl N2 O6 S; Mol wt: 456.9445

ACTION – An inhibitor of phospholipase A₂ (PLA₂; 77% inhibition at 0.1 μM) proven to reduce TPA-induced ear edema formation in mice by 86% when administered twice at a dose of 0.3 mg/ear. It also demonstrated analgesic activity in the mouse acetic acid-induced writhing test when given at a dose of 0.3 mg/kg i.p. Potentially useful as an antiinflammatory, antiallergic and/or immunomodulatory agent. Other compounds from this series of oxazolidine and thiazolidine derivatives are:



Compound	R1	R2	R3	A	B	Isomer	Formula
311630	Cl	H	6-Cl-3-Pyr-CH2	O	-N(NO2)-	trans	C ₁₆ H ₁₄ Cl ₂ N ₄ O ₃
311632	Cl	H	CONHN(Me)2	S	O	trans	C ₁₃ H ₁₆ ClN ₃ O ₂ S
311633	-(CH2)4-	6-MeO-2-THP-NHCO		O	O	cis	C ₂₁ H ₂₈ N ₂ O ₅
311634	Me	H	2-THP-NHCO	S	O	trans	C ₁₇ H ₂₂ N ₂ O ₃ S

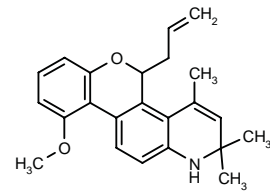
SOURCE – Nippon Soda.

REFERENCES

1. Takagi, M. et al. (Nippon Soda Co., Ltd.) *Oxa(thia)zolidine deriv. and anti-inflammatory drug.* WO 0172723.

311838

5-Allyl-10-methoxy-2,2,4-trimethyl-2,5-dihydro-1H-1-benzopyrano[3,4-f]quinoline



C23 H25 N O2; Mol wt: 347.4555

ACTION – Nonsteroidal selective glucocorticoid receptor modulator with nanomolar binding affinity for the α isoform of the human glucocorticoid receptor (hGR; K_i = 2.5 nM) and high selectivity over the progesterone receptor (K_i = 1800 nM). Compound was able to repress E-selectin transcription (EC₅₀ = 13 nM), with significantly reduced transcriptional activation of the ligand/glucocorticoid receptor complex. *In vivo*, it exhibited efficacy comparable to prednisolone in models of Sephadex-induced pulmonary eosinophilia in rats (ED₅₀ = 1.7 and 1.2 mg/kg p.o., respectively) and carrageenan-induced paw edema in rats (ED₅₀ = 15 and 4 mg/kg p.o., respectively). Potentially useful as an antiinflammatory agent.

SOURCES – Abbott; Ligand.

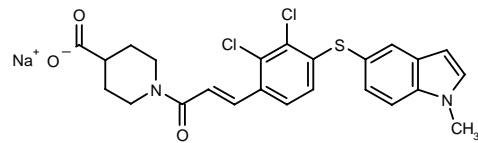
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1. Coughlan, M.J. et al. (Abbott Laboratories Inc.;Ligand Pharmaceuticals, Inc.) *Glucocorticoid-selective anti-inflammatory agents.* EP 1053239, WO 9941256.

2. Elmore, S.W. et al. *Nonsteroidal selective glucocorticoid modulators: The effect of C-5 alkyl substitution on the transcriptional activation/repression profile of 2,5-dihydro-10-methoxy-2,2,4-trimethyl-1H-[1]benzopyrano[3,4-f]quinolines.* J Med Chem 2001, 44(25): 4481.

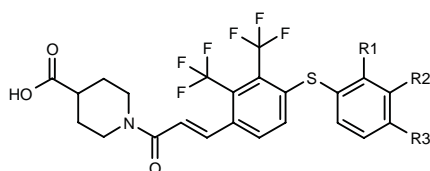
311858

1-[3-[2,3-Dichloro-4-(1-methyl-1H-indol-5-ylsulfanyl)-phenyl]-2(E)-propenoyl]piperidine-4-carboxylic acid sodium salt



C24 H21 Cl2 N2 Na O3 S; Mol wt: 511.4029

ACTION – An inhibitor of the leukocyte function-associated antigen-1 (LFA-1)/intercellular-adhesion molecule-1 (ICAM-1) interaction (IC₅₀ = 6 and 4 nM, respectively, in biochemical and cellular assays) proven to significantly inhibit eosinophilia (1-10 mg/kg p.o.) in a model of allergen-induced pulmonary inflammation in mice, and to inhibit neutrophil migration in a *Staphylococcus* enterotoxin A-induced neutrophil trafficking model in rats (50 and 100 mg/kg p.o.). A favorable pharmacokinetic profile was seen in rats, with an oral bioavailability of 60%. Potentially useful for the treatment of inflammatory diseases, autoimmune diseases, tumor metastases and reperfusion injury. Other related compounds are:



Compound	R1	R2	R3	Formula
311859	H	-OCH ₂ O-		C ₂₄ H ₁₉ F ₆ NO ₅ S
311860	OMe	H	H	C ₂₄ H ₂₁ F ₆ NO ₄ S

SOURCE – Abbott.

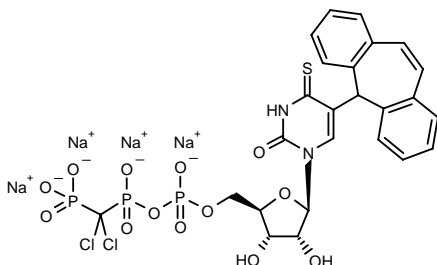
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- Link, J. et al. (Abbott Laboratories Inc.) *Cell adhesion-inhibiting antiinflammatory and immune-suppressive cpds.* EP 1165505, WO 0059880.
- Link, J. et al. (Abbott Laboratories Inc.) *Cell adhesion-inhibiting antiinflammatory and immune-suppressive cpds.* US 6110922, WO 0039081.
- Winn, M. et al. *Discovery of novel p-arylthio cinnamides as antagonists of leukocyte function-associated antigen-1/intercellular adhesion molecule-1 interaction. 4. Structure-activity relationships of substituents on the benzene ring of the cinnamide.* J Med Chem 2001, 44(25): 4393.

AR-C85095MX

311413

5-(5*H*-Dibenzo[*a,d*]cyclohepten-5-yl)-5'-*O*-[[[(1,1-dichloro-1-phosphonomethyl)(hydroxy)phosphoryloxy]](hydroxy)-phosphoryl]-4-thiouridine tetrasodium salt



C₂₅ H₂₁ Cl₂ N₂ Na₄ O₁₃ P₃ S; Mol wt: 845.2959

ACTION – Potent and selective P₂Y₂ receptor antagonist with a pA₂ value of 8.5 for inhibition of the uridine-5'-triphosphate (UTP)-induced increase in intracellular calcium in Jurkat cells stably transfected with cloned human P₂Y₂ receptors. Potentially useful as an anti-inflammatory agent.

SOURCE – AstraZeneca.

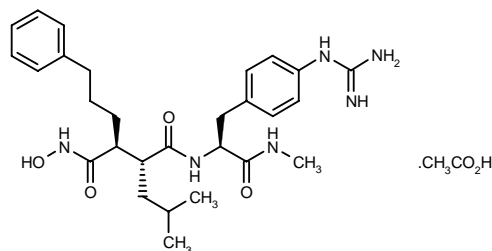
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- Kindon, N. et al. *SAR leading to the discovery of AR-C 85095MX, a potent and selective P₂Y₂ antagonist.* 11th RSC-SCI Med Chem Symp (Sept 9-12, Cambridge) 2001, Abst P8.
- Meghani, P. *The design of P₂Y₂ antagonists for the treatment of inflammatory diseases.* 11th RSC-SCI Med Chem Symp (Sept 9-12, Cambridge) 2001, Abst.

FYK-1388

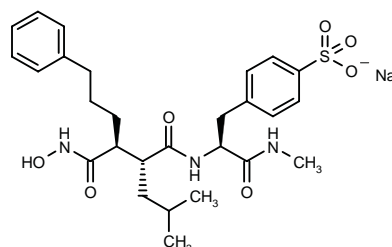
311259

*N*¹-[2-(4-Guanidinophenyl)-1-(*S*)-(N-methylcarbamoyl)-ethyl]-*N*⁴-hydroxy-2(*R*)-isobutyl-3(*S*)-(3-phenylpropyl)succinamide acetate



C₂₈ H₄₀ N₆ O₄ . C₂ H₄ O₂; Mol wt: 584.7136

ACTION – Broad-spectrum inhibitor of matrix metalloproteinases (MMPs) including interstitial collagenase (MMP-1; IC₅₀ = 6 nM), gelatinase A (MMP-2; IC₅₀ = 2 nM), stromelysin 1 (MMP-3; IC₅₀ = 6 nM), matrilysin (MMP-7; IC₅₀ = 0.7 nM), gelatinase B (MMP-9; IC₅₀ = 1 nM), macrophage elastase (MMP-12; IC₅₀ = 0.064 nM), MMP-13 (collagenase 3; IC₅₀ = 0.07 nM) and MMP-14 (MT-1 MMP; IC₅₀ = 4 nM), as well as TACE (TNF-α-converting enzyme; IC₅₀ = 130 nM). Compound exhibited a good plasma half-life (2.0 h) and significantly inhibited hindpaw swelling and bone destruction after just 3-7 days of dosing at 30 mg/kg/day s.c. in rats with adjuvant-induced arthritis. Potentially useful as an antiarthritic agent. Another related compound is:



FYK-1352 [311258]: C₂₇ H₃₆ N₃ Na O₇ S

SOURCE – Fuji Yakuhin.

REFERENCES

- Fujisawa, T. et al. (Fuji Yakuhin Kogyo Co., Ltd.) *Highly water-soluble metalloproteinase inhibitor.* EP 0832875, WO 9633968.
- Igeta, K. et al. (Fuji Yakuhin Kogyo Co., Ltd.; Maruho Co., Ltd.) *Therapeutic agents for allergic diseases.* EP 1101496, WO 0003734.
- Fujisawa, T. et al. *Development of highly water-soluble matrix metalloproteinases inhibitors.* 21st Symp Med Chem (Nov 28-30, Kyoto) 2001, Abst 2P-08.

MAB 175-62

310446*Anti-C2a monoclonal antibody*

ACTION – A monoclonal antibody specific to complement C2 and its activation factor C2a. This antibody is effective in inhibiting both the classical and the leptin complement pathways and is expected to be useful for the treatment of disorders related to excessive activation of the complement system such as inflammatory and autoimmune diseases. MAb 175-62 demonstrated a strong reactivity with human C2a in an ELISA assay and inhibited classical and alternative pathway hemolysis when tested in human serum.

SOURCE – Tanox.

REFERENCES

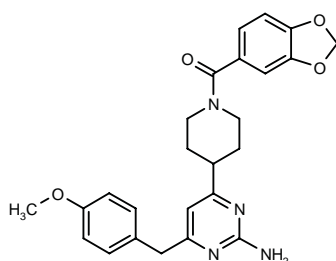
1. Fung, M. et al. (Tanox, Inc.) *Anti-C2/C2a inhibitors of complement activation*. WO 0170818.

SM-18163

311255

4-[1-(1,3-Benzodioxol-5-ylcarbonyl)piperidin-4-yl]-6-(4-methoxybenzyl)pyrimidin-2-amine

1-[4-[2-Amino-6-(4-methoxybenzyl)pyrimidin-4-yl]-piperidin-1-yl]-1-(1,3-benzodioxol-5-yl)methanone



C₂₅ H₂₆ N₄ O₄; Mol wt: 446.5044

ACTION – An inhibitor of TNF- α production (IC_{50} = 0.6 μ M in murine macrophages stimulated with lipopolysaccharide) with prophylactic and therapeutic efficacy in a mouse model of collagen-induced arthritis.

SOURCE – Sumitomo Pharmaceuticals.

REFERENCES

1. Fujiwara, N. et al. (Sumitomo Pharmaceuticals Co., Ltd.) *Piperidinylpyrimidine derivs*. EP 0892795, JP 2001511764, US 5948786, WO 9738992.

2. Fujiwara, N. et al. *Synthesis and bioactivities of novel piperidinylpyrimidine derivatives: Inhibitors of tumor necrosis factor- α production*. Bioorg Med Chem Lett 2000, 10(12): 1317.

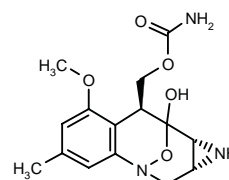
3. Fujiwara, N. et al. *Synthesis and structure-activity relationships of novel piperidinylpyrimidine derivatives: Inhibitors of tumor necrosis factor- α production*. 21st Symp Med Chem (Nov 28-30, Kyoto) 2001, Abst 2P-23.

ONCOLYTIC DRUGS

ANTIBIOTICS AND ALKALOIDS

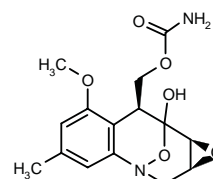
310856

Carbamic acid (1a*R*,8*S*,9a*R*)-9-hydroxy-7-methoxy-5-methyl-1,1a,2,8,9,9a-hexahydro-3,9-epoxyazirino[2,3-*c*]-[1]benzazocin-8-ylmethyl ester



C₁₅ H₁₉ N₃ O₅; Mol wt: 321.3311

ACTION – Antineoplastic antibiotic, an analogue of FR-900482, found to have an IC_{50} of 0.23 μ g/ml when tested for inhibition of human leukemia U-937 cell growth. Another exemplified compound is:



310857: C₁₅ H₁₈ N₂ O₆

SOURCE – Japan Science and Technology.

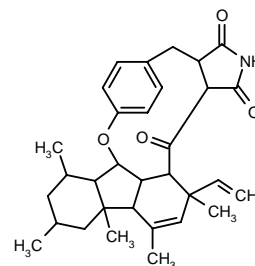
REFERENCES

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GKK-1032B

310849

10,12,13a,14,16-Pentamethyl-16-vinyl-3,3a,4,9a,9b,10,11,12,13,13a,13b,16,16a,16b,17,17a-hexadecahydro-1*H*-5,8-ethenofluoreno[9',1':2,3,4]oxacyclododecino-[6,7-*c*]pyrrole-1,3,17-trione



C₃₂ H₃₉ N O₄; Mol wt: 501.6631

MAB 175-62

310446*Anti-C2a monoclonal antibody*

ACTION – A monoclonal antibody specific to complement C2 and its activation factor C2a. This antibody is effective in inhibiting both the classical and the leptin complement pathways and is expected to be useful for the treatment of disorders related to excessive activation of the complement system such as inflammatory and autoimmune diseases. MAb 175-62 demonstrated a strong reactivity with human C2a in an ELISA assay and inhibited classical and alternative pathway hemolysis when tested in human serum.

SOURCE – Tanox.

REFERENCES

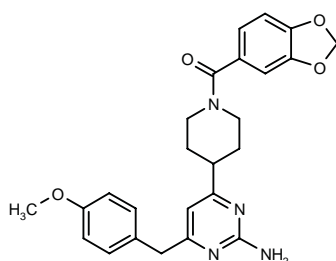
1. Fung, M. et al. (Tanox, Inc.) *Anti-C2/C2a inhibitors of complement activation*. WO 0170818.

SM-18163

311255

4-[1-(1,3-Benzodioxol-5-ylcarbonyl)piperidin-4-yl]-6-(4-methoxybenzyl)pyrimidin-2-amine

1-[4-[2-Amino-6-(4-methoxybenzyl)pyrimidin-4-yl]-piperidin-1-yl]-1-(1,3-benzodioxol-5-yl)methanone



C₂₅ H₂₆ N₄ O₄; Mol wt: 446.5044

ACTION – An inhibitor of TNF- α production (IC_{50} = 0.6 μ M in murine macrophages stimulated with lipopolysaccharide) with prophylactic and therapeutic efficacy in a mouse model of collagen-induced arthritis.

SOURCE – Sumitomo Pharmaceuticals.

REFERENCES

1. Fujiwara, N. et al. (Sumitomo Pharmaceuticals Co., Ltd.) *Piperidinylpyrimidine derivs*. EP 0892795, JP 2001511764, US 5948786, WO 9738992.

2. Fujiwara, N. et al. *Synthesis and bioactivities of novel piperidinylpyrimidine derivatives: Inhibitors of tumor necrosis factor- α production*. Bioorg Med Chem Lett 2000, 10(12): 1317.

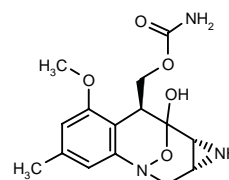
3. Fujiwara, N. et al. *Synthesis and structure-activity relationships of novel piperidinylpyrimidine derivatives: Inhibitors of tumor necrosis factor- α production*. 21st Symp Med Chem (Nov 28-30, Kyoto) 2001, Abst 2P-23.

ONCOLYTIC DRUGS

ANTIBIOTICS AND ALKALOIDS

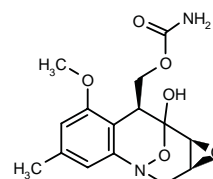
310856

Carbamic acid (1a*R*,8*S*,9a*R*)-9-hydroxy-7-methoxy-5-methyl-1,1a,2,8,9,9a-hexahydro-3,9-epoxyazirino[2,3-*c*]-[1]benzazocin-8-ylmethyl ester



C₁₅ H₁₉ N₃ O₅; Mol wt: 321.3311

ACTION – Antineoplastic antibiotic, an analogue of FR-900482, found to have an IC_{50} of 0.23 μ g/ml when tested for inhibition of human leukemia U-937 cell growth. Another exemplified compound is:



310857: C₁₅ H₁₈ N₂ O₆

SOURCE – Japan Science and Technology.

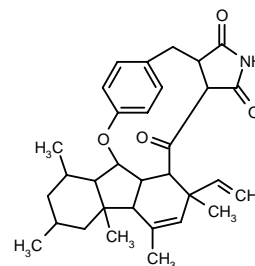
REFERENCES

1. Fukuyama, T. and Tokuyama, H. (Japan Science and Technology Corp.) *FR900482 analogues and their preparation method*. JP 2001247573.

GKK-1032B

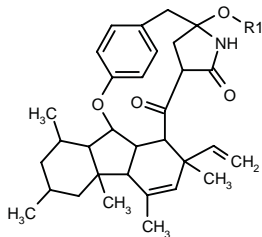
310849

10,12,13a,14,16-Pentamethyl-16-vinyl-3,3a,4,9a,9b,10,11,12,13,13a,13b,16,16a,16b,17,17a-hexadecahydro-1*H*-5,8-ethenofluoreno[9',1':2,3,4]oxacyclododecino[6,7-*c*]pyrrole-1,3,17-trione



C₃₂ H₃₉ N O₄; Mol wt: 501.6631

ACTION – Antitumor and antibacterial agent isolated from a culture of *Penicillium* sp. GKK 1032 (FERM BP-6834), proven active against *Bacillus subtilis* No. 10707 (MIC = 20.8 µg/ml) and to inhibit the proliferation of human cervical cancer-derived HeLa S3 cells with an IC₅₀ of 17.7 µM. Other compounds from the same source are:



Compound	R1	Formula
GKK-1032A1 [310853]	Me	C ₃₃ H ₄₃ NO ₄
GKK-1032A2 [310854]	H	C ₃₂ H ₄₁ NO ₄
GKK-1032A3 [310855]	Et	C ₃₄ H ₄₅ NO ₄

SOURCE – Kyowa Hakko.

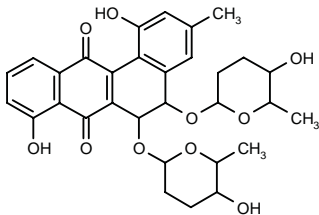
REFERENCES

1. Koizumi, F. et al. (Kyowa Hakko Kogyo Co., Ltd.) *Physiologically active substance GKK1032 cpds.* JP 2001247574.

J-124131

311481

1,8-Dihydroxy-5,6-bis(5-hydroxy-6-methyltetrahydropyran-2-yloxy)-3-methyl-5,6,7,12-tetrahydrobenzo[a]-anthracene-7,12-dione



C31 H34 O10; Mol wt: 566.5996

ACTION – Antitumor agent isolated from a culture of *Streptomyces* sp. A74169 (FERM P-16924). Compound inhibited the proliferation of murine leukemia P388 cells and human colon cancer DLD-1 cells with respective IC₅₀ values of 0.15 and 0.27 µg/ml.

SOURCE – Banyu.

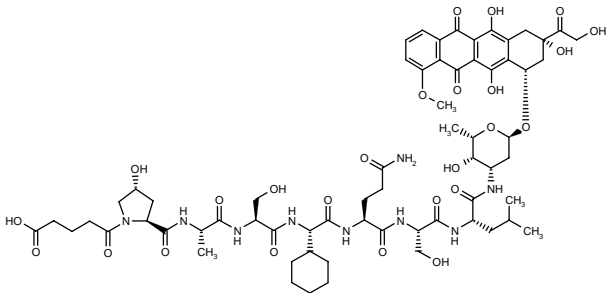
REFERENCES

1. Naito, S. et al. (Banyu Pharmaceutical Co., Ltd.) *Anti-tumor substance J-124131 and its preparation method.* JP 2001261668.

L-377202

289448

N-[*N*-(4-Carboxybutyryl)-4(*R*)-hydroxy-L-prolyl-L-alanyl-L-seryl-L-cyclohexylglycyl-L-glutaminy-L-seryl-L-leucyl]doxorubicin



C65 H89 N9 O25; Mol wt: 1396.4560

ACTION – Doxorubicin prodrug consisting of doxorubicin conjugated with a peptide hydrolyzable by prostate-specific antigen (PSA), proven to be much less toxic than doxorubicin against non-PSA-secreting cells. The conjugate exhibited > 27-fold selectivity for human prostate cancer PSA-secreting LNCaP cells relative to the non-PSA-secreting DuPRO cell line (EC₅₀ = 5 and > 100 µM, respectively). In mice bearing LNCaP tumors, compound at a dose of 21.5 µmol/kg i.p. reduced PSA levels by 95% and tumor weight by 87% and was about 15-fold more effective than doxorubicin. Phase I and II trials demonstrated that the conjugate is well tolerated in patients with hormone-refractory prostate cancer and that it was cleaved to produce detectable levels of doxorubicin or Leu-doxorubicin. Potentially useful for the treatment of prostate cancer.

SOURCE – Merck & Co.

REFERENCES

1. DeFeo-Jones, D. et al. (Merck & Co., Inc.) *A method of treating cancer.* WO 0059930.

2. Garsky, V.M. et al. (Merck & Co., Inc.) *Conjugates useful in the treatment of prostate cancer.* JP 2000509407, WO 9818493.

3. Karki, S.B. et al. (Merck & Co., Inc.) *Salt form of a conjugate useful in the treatment of prostate cancer.* WO 0130804.

4. DeFeo-Jones, D. et al. *A peptide-doxorubicin "prodrug" activated by prostate-specific antigen selectively kills prostate tumor cells positive for prostate-specific antigen in vivo.* Nat Med 2000, 6(11): 1248.

5. DiPaola, R.S. et al. *A phase I and II trial of a PSA activated peptide-doxorubicin conjugate, with and without prednisone, in patients with hormone refractory prostate cancer.* Proc Am Soc Clin Oncol 2001, 20(Part 1): Abst 727.

6. DiPaola, R.S. et al. *Phase I and pharmacokinetic study of L377202, a novel peptide doxorubicin conjugate, in patients with advanced prostate cancer.* Proc Am Soc Clin Oncol 2000, 19: Abst 1370.

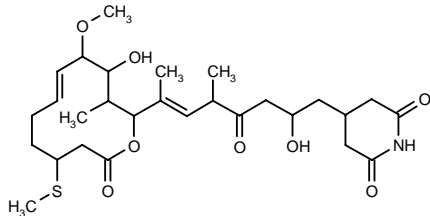
7. Garsky, V.M. et al. *Design and synthesis of a selective PSA cleavable peptide-doxorubicin prodrug which targets PSA positive tumor cells.* 17th Am Peptide Symp (June 9-14, San Diego) 2001, Abst L22.

8. Garsky, V.M. et al. *The synthesis of a prodrug of doxorubicin designed to provide reduced systemic toxicity and greater target efficacy.* J Med Chem 2001, 44(24): 4216.

NK-30424F

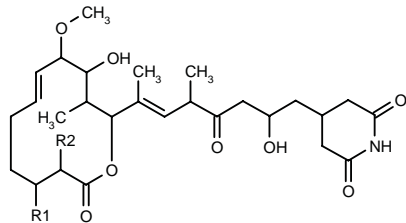
311524

4-[2-Hydroxy-7-[4-hydroxy-5-methoxy-3-methyl-10-(methylsulfanyl)-12-oxooxacyclododec-6-en-2-yl]-5-methyl-4-oxo-6-octenyl]piperidine-2,6-dione isomer A



C28 H43 N O8 S; Mol wt: 553.7127

ACTION – Antineoplastic agent isolated from cultures of *Streptomyces* sp. NA30424 (FERM P-16422). It was shown to inhibit the proliferation of murine leukemia J774.1 cells and human breast cancer MDA-MB-231 and MDA-MB-468, colon cancer HCT 116 and lung cancer NCI-H460 cells with IC₅₀ values of 0.085, 0.12, 0.083, 0.009 and 0.032 μM, respectively. Other compounds from the same source are:



Compound	R1	R2	Isomer	Formula
NK-30424G [311525]	SMe	H	B	C ₂₈ H ₄₃ NO ₈ S
NK-30424C [311526]	bond			C ₂₇ H ₃₉ NO ₈

SOURCE – Nippon Kayaku.

REFERENCES

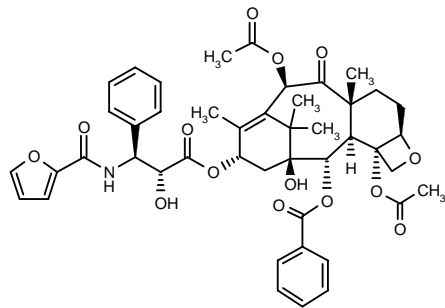
1. Takayasu, Y. et al. (Nippon Kayaku Co., Ltd.) *Physiologically active substance NK30424 analogues, their preparation method and use.* JP 2001278883.

ANTIMITOTIC DRUGS

310838

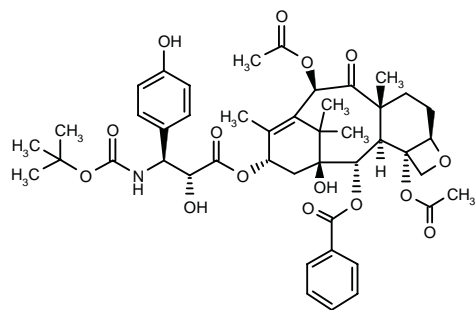
3'-N-Debenzoyl-7-deoxy-3'-N-(furan-2-ylcarbonyl)-paclitaxel

(2a*R*,4a*R*,6*R*,9*S*,11*S*,12*S*,12a*R*,12b*S*)-6,12b-Diacetoxy-12-(benzoyloxy)-9-[3(*S*)-(furan-2-ylcarboxamido)-2(*R*)-hydroxy-3-phenylpropionyloxy]-11-hydroxy-4a,8,13,13-tetramethyl-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-1*H*-7,11-methanocyclodeca[3,4]benzo[1,2-*b*]oxet-5-one



C45 H49 N O14; Mol wt: 827.8751

ACTION – Antitumor taxane derivative found to inhibit the proliferation of the human colon cancer cell line HCT 116 with an IC₅₀ of 0.85 nM. In *in vivo* testing, it displayed antitumor activity comparable to paclitaxel when administered to mice bearing s.c.-implanted murine lung carcinoma M109 xenografts. Unlike the reference compound, it was active following either i.v. or p.o. administration. Another exemplified 7-deoxytaxane derivative is:



310839: C45 H55 N O15

SOURCE – Bristol-Myers Squibb.

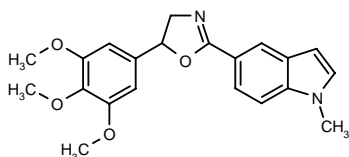
REFERENCES

1. Kadow, J.F. et al. (Bristol-Myers Squibb Co.) *Taxane anticancer agents.* WO 0170718.

A-259745*

301979

1-Methyl-5-[5-(3,4,5-trimethoxyphenyl)-4,5-dihydro-oxazol-2-yl]-1*H*-indole



C21 H22 N2 O4; Mol wt: 366.4148

ACTION – Antimitotic agent, an indolyloxazoline with strong *in vitro* activity against multidrug-resistant (MDR) human colon adenocarcinoma HCT-15 cells and MDR-negative human non-small cell lung carcinoma NCI-H460 cells (ED_{50} = 0.018 and 0.028 μ M, respectively). *In vivo* in mice bearing reticulum cell sarcoma M5076, a dose of 50 mg/kg/day p.o. was effective in increasing survival time, in contrast to paclitaxel, vincristine and A-105972 which were inactive; when it was administered at doses of 25 and 50 mg/kg/day p.o. for 28 days, a dose-dependent increase in mean survival time (120 and 227%, respectively) was observed. Compound exhibited a favorable pharmacokinetic profile in rats with 35% oral bioavailability and a half-life of 1.9 h.

SOURCE – Abbott.

REFERENCES

1. Gwaltney, S.L. II et al. (Abbott Laboratories Inc.) *Oxazoline antiproliferative agents*. US 6228868.
2. Gwaltney, S.L. II et al. (Abbott Laboratories Inc.) *Substd. oxazolines as antiproliferative agents*. WO 0006556.
3. Gwaltney, S.L. II et al. *Potent, bioavailable, and efficacious oxazoline antimitotic agents*. 221st ACS Natl Meet (April 1-5, San Diego) 2001, Abst MEDI 157.
4. Liu, G. et al. *Antimitotic agents with activity in multidrug-resistant tumor cell lines*. 221st ACS Natl Meet (April 1-5, San Diego) 2001, Abst MEDI 139.
5. Szczepankiewicz, B.G. et al. *New antimitotic agents with activity in multi-drug-resistant cell lines and in vivo efficacy in murine tumor models*. J Med Chem 2001, 44(25): 4416.

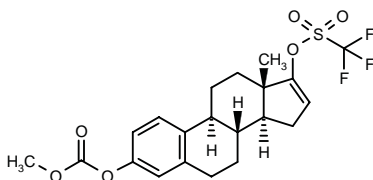
*Identified compound **301979** Drug Data Rep 2001, 023(06): 0597.

HORMONAL AGENTS

310283

Trifluoromethanesulfonic acid 3-(methoxycarbonyloxy)-estra-1,3,5(10),16-tetraen-17-yl ester

Methyl 17-(trifluoromethylsulfonyloxy)estra-1,3,5(10),16-tetraen-3-yl carbonate



C21 H23 F3 O6 S; Mol wt: 460.4667

ACTION – A representative compound from a series of steroid derivatives with steroid sulfatase-inhibitory activity, potentially useful for the treatment of estrogen-dependent breast cancer.

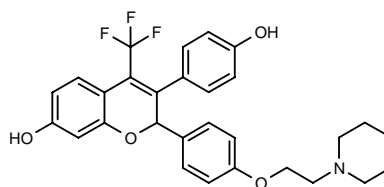
SOURCE – Kuraray.

REFERENCES

1. Nakazawa, M. et al. (Kuraray Co., Ltd.) *Steroid derivs. and process for producing the same*. WO 0166562.

310371

(+)-3-(4-Hydroxyphenyl)-2-[4-[2-(1-piperidinyl)ethoxy]-phenyl]-4-(trifluoromethyl)-2*H*-1-benzopyran-7-ol



C29 H28 F3 N O4; Mol wt: 511.5372

ACTION – Antiestrogenic agent that displays bone-protecting activity in ovariectomized rats at an oral dose of 0.1 mg/kg/day. Potentially useful for the treatment of hormone-dependent diseases and tumors, in hormone replacement therapy and for the treatment of osteoporosis.

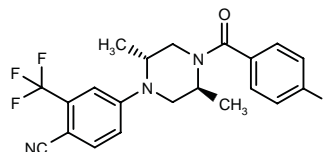
SOURCE – Schering AG.

REFERENCES

1. Künzer, H. et al. (Schering AG) *4-Fluoroalkyl-2H-benzopyrans with anti-estrogenic activity*. WO 0168634.

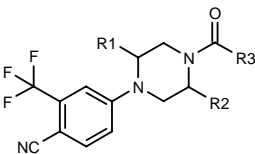
311505

4-[(2*R**,5*S**)-4-(4-Fluorobenzoyl)-2,5-dimethylpiperazin-1-yl]-2-(trifluoromethyl)benzonitrile

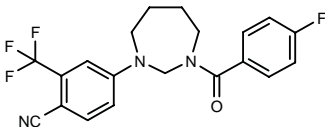


C21 H19 F4 N3 O; Mol wt: 405.3931

ACTION – Antiandrogenic agent, potentially useful in the treatment of prostate cancer, prostatic hypertrophy, baldness, acne, seborrhea, hypertrichosis and other androgen-dependent diseases. Other exemplified cyanophenyl derivatives are:



Compound	R1	R2	R3	Isomer	Formula
311506	H	H	4-F-Ph		C ₁₉ H ₁₅ F ₄ N ₃ O
311507	Me	H	3-Pyr		C ₁₉ H ₁₇ F ₃ N ₄ O
311508	Me	Me	4-F-PhCH2	2S,5R	C ₂₂ H ₂₁ F ₄ N ₃ O
311509	Me	Me	3,4-(Cl)2-Ph	2R*,5S*	C ₂₁ H ₁₈ Cl ₂ F ₃ N ₃ O
311510	Me	Me	2-Pyr-CH2	2R*,5S*	C ₂₁ H ₂₁ F ₃ N ₄ O
311511	Me	Me	3-Pyr-CH2OCH2	2S,5R	C ₂₂ H ₂₃ F ₃ N ₄ O ₂
311513	Me	Me	4-Pip-CH2	2S,5R	C ₂₁ H ₂₇ F ₃ N ₄ O



311512: C20 H17 F4 N3 O

SOURCE – Yamanouchi.

REFERENCES

1. Taniguchi, N. et al. (Yamanouchi Pharmaceutical Co., Ltd.) *Cyanophenyl derivs.* JP 2001261657.

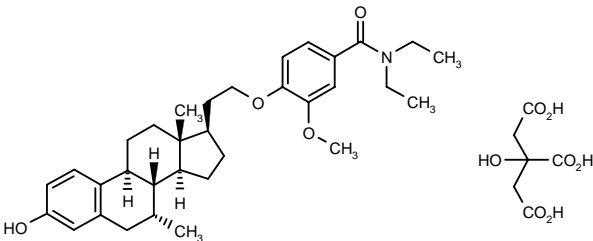
TAS-108

282708

N,N-Diethyl-4-[2-(3-hydroxy-7 α -methylestra-1,3,5(10)-trien-17 β -yl)ethoxy]-3-methoxybenzamide citrate

N,N-Diethyl-4-(3-hydroxy-7 α -methyl-19-norpregna-1,3,5(10)-trien-21-yloxy)-3-methoxybenzamide citrate

SR-16233 (as free base)
SR-16234



C33 H45 N O4 . C6 H8 O7; Mol wt: 711.8437

ACTION – Orally active selective estrogen receptor modulator (SERM) with improved tissue-selective agonist activity in the bone and cardiovascular tissue compared with tamoxifen, raloxifene and EM-800, and estrogen-antagonist activity in breast tumors and the uterus. Compound exhibited strong anticancer activity, superior to that of fulvestrant (Faslodex), in tamoxifen-resistant breast cancer cells and pure antiuterotrophic activity. In a phase I trial in healthy postmenopausal women, the tolerability and pharmacokinetics of single ascending doses of compound (10-160 mg) in the fasting state, and of a dose of 120 mg after a high-fat meal, were evaluated. Compound was readily absorbed after oral doses of 80-160 mg and pharmacokinetics were dose-dependent,

plasma levels declining monoexponentially with a mean half-life of 3.04-4.43 h; food markedly increased the bioavailability of compound but had no effect on the half-life. No serious adverse events were observed. Potentially useful for the treatment of breast cancer.

SOURCES – SRI; Taiho.

REFERENCES

1. Peters, R.H. et al. (SRI International) *Synthesis of anti-estrogenic acid and other therapeutic steroids from 21-hydroxy-19-norpregna-4-en-3-one*. WO 0158919.

2. Kuritani, J. et al. *Phase I study of the novel oral steroidal antiestrogenic agent TAS-108, ascending single dose, safety, tolerance, and pharmacokinetic parameters in healthy postmenopausal women*. 24th Annu San Antonio Breast Cancer Symp (Dec 10-13, San Antonio) 2001, Abst 456.

3. Tanabe, M. et al. *SR 16234, a novel steroidal tissue selective antiestrogen: Selective estrogen receptor modulator (SERM)*. AACR-NCI-EORTC Int Conf Mol Targets Cancer Ther (Nov 16-19, Washington) 1999, Abst 563.

4. Toko, T. et al. *Estrogenic/antiestrogenic activities of SR16234, a new antiestrogenic agent*. Jpn J Cancer Res 1999, 90(Suppl.): Abst 2269.

5. Yamamoto, Y. et al. *Distinct modulation of ER- α , β -mediated activity by TAS-108 (SR-16234) may lead to unique intranuclear events in tumor, uterine and other normal tissues*. 24th Annu San Antonio Breast Cancer Symp (Dec 10-13, San Antonio) 2001, Abst 454.

6. Yamamoto, Y. et al. *Molecular mechanism of actions of TAS-108 (SR-16234), a novel steroidal selective estrogen receptor modulator (SERM)*. Proc Amer Assoc Cancer Res 2001, 42: Abst 1453.

7. Yamamoto, Y. et al. *Molecular mechanism of actions of TAS-108 (SR16234), a novel steroidal antiestrogen*. Jpn J Cancer Res 2001, 92(Suppl.): Abst 2078.

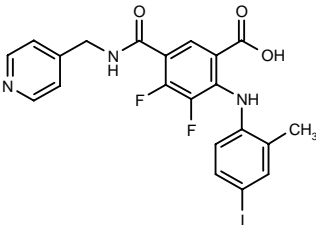
8. *Taiho obtains exclusive worldwide rights to potential breast cancer treatment*. DailyDrugNews.com (Daily Essentials) 1999, July 6.

INHIBITORS OF SIGNAL
TRANSDUCTION PATHWAYS

310411

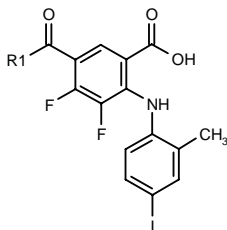
3,4-Difluoro-2-(4-iodo-2-methylphenylamino)-5-[*N*-(pyridin-4-ylmethyl)carbamoyl]benzoic acid

4,5-Difluoro-6-(4-iodo-2-methylphenylamino)-*N*-(pyridin-4-ylmethyl)isophthalamic acid



C21 H16 F2 I N3 O3; Mol wt: 523.2714

ACTION – Mitogen ERK kinase (MEK) inhibitor, potentially useful for the treatment of proliferative diseases including cancer (particularly brain, breast, lung, ovarian, pancreatic, prostate, renal or colorectal cancer), psoriasis, arthritis, heart failure, chronic pain (including neuropathic and idiopathic pain, and pain associated with alcoholism, vitamin deficiency, uremia and hypothyroidism), restenosis, autoimmune diseases and atherosclerosis. Other exemplified 5-amide substituted diaryl-amines include the following:



Compound	R1	Formula
310413	2(S)-OH-cyclohexyl-NH	C ₂₁ H ₂₁ F ₂ IN ₂ O ₄
310414	4-[3-(PhO)-4-Pyr]-perhydro-1,4-diazepin-1-yl	C ₃₁ H ₂₇ F ₂ IN ₄ O ₄
310415	4-(3-Me-2-quinoxaliny)-1-Piz	C ₂₈ H ₂₄ F ₂ IN ₅ O ₃
310416	cyclohexyl-NH(CH ₂) ₃ NH	C ₂₄ H ₂₈ F ₂ IN ₃ O ₃

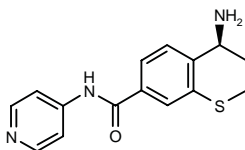
SOURCE – Pfizer.

REFERENCES

1. Biwersi, C. et al. (Pfizer Inc.) 5-Amide subst. diarylamines as MEK inhibitors. WO 0168619.

310930

4(S)-Amino-N-(4-pyridyl)-3,4-dihydro-2H-1-benzothio-pyran-7-carboxamide



C₁₅ H₁₅ N₃ O S; Mol wt: 285.3695

ACTION – A potent and selective Rho kinase inhibitor (IC₅₀ = 13 nM) with good pharmacokinetic properties. Potentially useful for the treatment of cancer, hypertension, pulmonary hypertension, angina pectoris, asthma, peripheral vascular disorders, preterm labor, arteriosclerosis, inflammation, pain, autoimmune diseases, AIDS, retinopathy, bone resorption disorders, glaucoma, fibrosis, erectile dysfunction, and ischemic and reperfusion disorders.

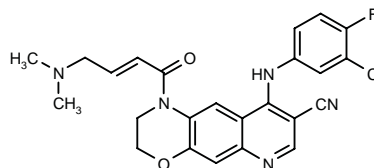
SOURCE – Mitsubishi Pharma.

REFERENCES

1. Takanashi, S. et al. (Welfide Corp.) Amide cpds. and use thereof. WO 0168607.

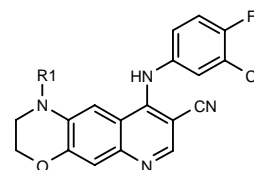
311089

9-(3-Chloro-4-fluorophenylamino)-1-[4-(dimethylamino)-2(E)-butenoyl]-2,3-dihydro-1H-[1,4]oxazino[3,2-g]-quinoline-8-carbonitrile



C₂₄ H₂₁ Cl F N₅ O₂; Mol wt: 465.9139

ACTION – Protein tyrosine kinase inhibitor with an IC₅₀ of 0.17 nM against epidermal growth factor (EGF) receptor kinase. It inhibited the proliferation of several cancer cell lines and the growth of human epidermoid cancer A-431 xenografts in mice. Potentially useful for the treatment of cancer and polycystic kidney disease. Other exemplified compounds from this series include the following:



Compound	R1	Formula
311090	H	C ₁₈ H ₁₂ ClFN ₄ O
311092	(E)-COCH=CHCH ₂ Cl	C ₂₂ H ₁₅ Cl ₂ FN ₄ O ₂
311093	(E)-COCH=CHCH ₂ Br	C ₂₂ H ₁₅ BrClFN ₄ O ₂
311094	CO(CH ₂) ₃ N(Me) ₂	C ₂₄ H ₂₃ ClFN ₅ O ₂
311095	(CH ₂) ₄ Cl	C ₂₂ H ₁₉ Cl ₂ FN ₄ O
311096	(CH ₂) ₄ N(Me) ₂	C ₂₄ H ₂₅ ClFN ₅ O

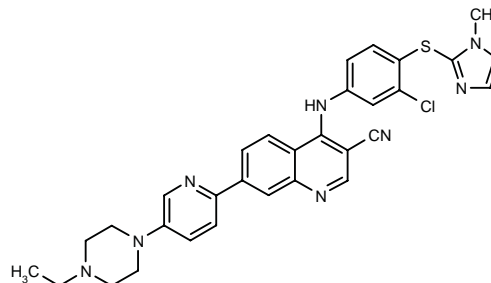
SOURCE – American Home Products.

REFERENCES

1. Tsou, H.-R. et al. (American Home Products Corp.) Tricyclic protein kinase inhibitors. WO 0172758.

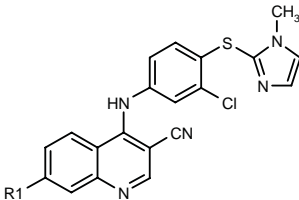
311097

4-[3-Chloro-4-(1-methyl-1H-imidazol-2-yl)sulfanyl]phenyl-amino]-7-[5-(4-ethylpiperazin-1-yl)pyridin-2-yl]quinoline-3-carbonitrile



C₃₁ H₂₉ Cl N₈ S; Mol wt: 581.1451

ACTION – Protein tyrosine kinase inhibitor with an IC₅₀ of 1.5 nM against Raf1 kinase. It inhibited the proliferation of human adenocarcinoma LoVo and Caco-2 cells (IC₅₀ = 0.0026 and 0.39 μM, respectively). Potentially useful for the treatment of cancer and polycystic kidney disease. Other exemplified compounds from this series of 3-cyano-naphthyridine and 3-cyanoquinoline derivatives include the following:



Compound	R1	Formula
311098	5-(4-OH-1-Pip-CH2)-2-thienyl	C ₃₀ H ₂₇ ClN ₆ OS ₂
311099	6-(4-Et-1-Piz)-3-Pyr	C ₃₁ H ₂₉ ClN ₆ S
311100	6-[4-(1-pyrrolidinyl)-1-Pip]-3-Pyr	C ₃₄ H ₃₃ ClN ₆ S

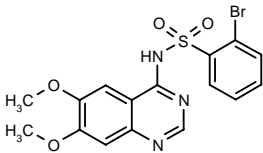
SOURCE – American Home Products.

REFERENCES

1. Boschelli, D.H. et al. (American Home Products Corp.) 3-Cyanoquinolines, 3-cyano-1,6-naphthyridine, and 3-cyano-1,7-naphthyridines as protein kinase inhibitors. WO 0172711.

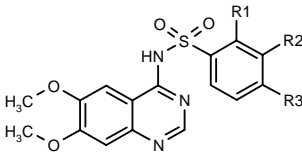
311132

2-Bromo-N-(6,7-dimethoxyquinazolin-4-yl)benzene-sulfonamide



C16 H14 Br N3 O4 S; Mol wt: 424.2736

ACTION – A selective inhibitor of class 1 receptor tyrosine kinases, especially epidermal growth factor (EGF) receptor kinase. By virtue of its activity, this compound is considered to have potential in the treatment of hyper-proliferative diseases including cancer, psoriasis, postangioplasty restenosis, atherosclerosis and kidney and liver fibrosis. Other specifically claimed fused bicyclic amines are:



Compound	R1	R2	R3	Formula
311133	I	H	H	C ₁₆ H ₁₄ N ₃ O ₄ S
311135	CN	H	H	C ₁₇ H ₁₄ N ₄ O ₄ S
311136	H	H	Br	C ₁₆ H ₁₄ BrN ₃ O ₄ S
311138	Cl	H	H	C ₁₆ H ₁₄ ClN ₃ O ₄ S
311140	H	Cl	H	C ₁₆ H ₁₄ ClN ₃ O ₄ S
311141	H	H	Cl	C ₁₆ H ₁₄ ClN ₃ O ₄ S
311143	H	H	OMe	C ₁₇ H ₁₇ N ₃ O ₅ S
311145	H	H	Me	C ₁₇ H ₁₇ N ₃ O ₄ S

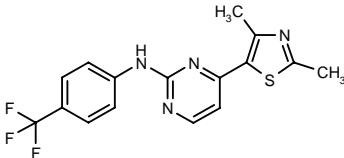
SOURCE – Celltech Group.

REFERENCES

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311169

4-(2,4-Dimethylthiazol-5-yl)-N-[4-(trifluoromethyl)phenyl]-pyrimidin-2-amine



C16 H13 F3 N4 S; Mol wt: 350.3667

ACTION – Antiproliferative agent, a cyclin-dependent kinase (CDK) inhibitor with high selectivity for CDK2 and CDK4. It exhibited cytotoxic activity against a variety of human tumor cells and induced cell cycle arrest and apoptosis in human osteosarcoma Saos-2 and lung carcinoma A549 cells.

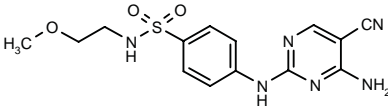
SOURCE – Cyclacel.

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1. Fischer, P.M. and Wang, S. (Cyclacel Ltd.) 2-Subst. 4-heteroaryl-pyrimidines and their use in the treatment of proliferative disorders. WO 0172745.

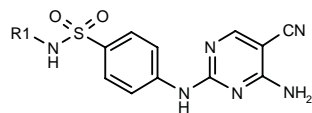
311315

4-(4-Amino-5-cyanopyrimidin-2-ylamino)-N-(2-methoxy-ethyl)benzenesulfonamide



C14 H16 N6 O3 S; Mol wt: 348.3854

ACTION – Cyclin-dependent kinase (CDK) inhibitor, particularly active against CDK2, CDK4 and/or CDK6. Potentially useful for the treatment of cancer. Other specifically claimed 4-amino-5-cyanopyrimidin-2-amines include the following:



Compound	R1	Formula
311316	2-THF-CH2	C ₁₆ H ₁₈ N ₆ O ₃ S
311317	4-F-PhCH2	C ₁₈ H ₁₅ FN ₆ O ₂ S
311318	(CH2)3OMe	C ₁₅ H ₁₈ N ₆ O ₃ S
311319	cyclopropyl	C ₁₄ H ₁₄ N ₆ O ₂ S
311320	allyl	C ₁₄ H ₁₄ N ₆ O ₂ S
311321	Pr	C ₁₄ H ₁₆ N ₆ O ₂ S
311322	i-PrNHCH2CH2	C ₁₆ H ₂₁ N ₇ O ₂ S
311323	i-PrNH(CH2)3	C ₁₇ H ₂₃ N ₇ O ₂ S
311324	1-Pip-CH2CH2	C ₁₈ H ₂₃ N ₇ O ₂ S

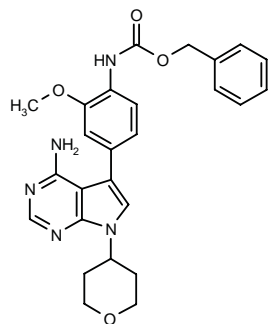
SOURCE – AstraZeneca.

REFERENCES

1. Thomas, A.P. (AstraZeneca AB;AstraZeneca plc) 4-Amino-5-cyano-2-anilino-pyrimidine derivs. and their use as inhibitors of cell-cycle kinases. WO 0172717.

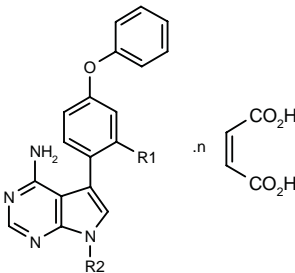
311349

N-[4-[4-Amino-7-(tetrahydropyran-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]-2-methoxyphenyl]carbamic acid benzyl ester

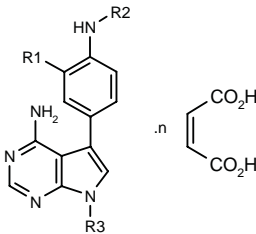


C26 H27 N5 O4; Mol wt: 473.5303

ACTION – Protein kinase inhibitor, potentially useful in a wide variety of hyperproliferative disorders including cancer, ulcers, viral infections, psoriasis, Paget’s disease, fibrosis, cirrhosis, chronic obstructive pulmonary disease, asthma, stroke, endometriosis, inflammatory bowel disease, arthritis, multiple sclerosis, transplant rejection, sickle cell anemia, ocular conditions, atherosclerosis, restenosis and diabetes. Other exemplified pyrrolo[2,3-d]pyrimidine derivatives include the following:



Compound	R1	R2	n	Formula
311350	H	(R)-CH2CONHCH2CH(OH)Me	0	C ₂₃ H ₂₃ N ₅ O ₃
311351	H	CH(Me)CONHCH2CH2N(Me)2	0	C ₂₅ H ₂₈ N ₆ O ₂
311352	H	3-CN-2-Pyr	0	C ₂₄ H ₁₆ N ₆ O
311353	Me	trans-4-(4-Me-1-Piz)-cyclohexyl	3	C ₃₀ H ₃₆ N ₆ O .3C ₄ H ₄ O ₄
311354	H	trans-4-[3(R)-N(Me)2- -1-pyrrolidinyl]-cyclohexyl	3	C ₃₀ H ₃₆ N ₆ O .3C ₄ H ₄ O ₄
311358	H	4-OH-4-(CH2NHCH2CH2- OCH2CH2OH)-cyclohexyl	0	C ₂₉ H ₃₅ N ₅ O ₄



Compound	R1	R2	R3	n	Formula
311355	F	2-Br-PhSO2	cis-4-(4-Me-1-Piz)- -cyclohexyl	3	C ₂₉ H ₃₃ BrFN ₇ O ₂ S .3C ₄ H ₄ O ₄
311357	OMe	3-MeO-PhCO	cis-4-(4-Me-1-Piz)- -cyclohexyl	0	C ₃₂ H ₃₉ N ₇ O ₃
311359	F	4-F-PhSO2	1-(1-Me-4-Pip)-4-Pip	0	C ₂₉ H ₃₃ F ₂ N ₇ O ₂ S

SOURCE – BASF.

REFERENCES

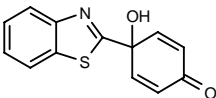
1. Hirst, G.C. et al. (BASF AG) Pyrrolopyrimidines as tyrosine kinase inhibitors. WO 0172751.

AW-464

311885

4-(2-Benzothiazolyl)-4-hydroxy-2,5-cyclohexadien-1-one

NSC-706704



C13 H9 N O2 S; Mol wt: 243.2851

ACTION – Antineoplastic agent, a thioredoxin inhibitor (IC₅₀ = 12 mM) proven able to induce apoptosis in acute myeloid leukemia (AML) cells at submicromolar concentrations. Compound was active against human renal and colon carcinoma cell lines *in vitro* and inhibited the growth of human renal carcinoma xenografts in mice by over 50% as two doses of 15 mg/kg i.p.

SOURCE – University of Nottingham, Nottingham (GB).

REFERENCES

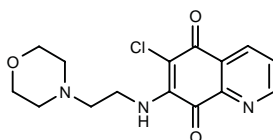
1. Pallis, M. et al. *Expression of thioredoxin in primary AML and induction of apoptosis by the thioredoxin-inhibitory compound AW464*. Blood 2001, 98(11, Part 1): Abst 437.

NSC-663284¹⁻³

302482

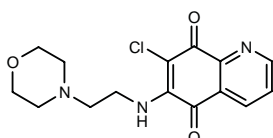
6-Chloro-7-[2-(4-morpholinyl)ethylamino]-5,8-dihydroquinoline-5,8-dione

DA-3003-1



C₁₅ H₁₆ Cl N₃ O₃; Mol wt: 321.7624

ACTION – Antineoplastic agent, a potent inhibitor of the dual-specificity protein-tyrosine-phosphatase Cdc25 (K_i = 29, 95 and 89 nM against Cdc25A, Cdc25B and Cdc25C, respectively) with 20- and 450-fold selectivity over VHR and PTP1B phosphatases, respectively. Compound showed strong cytotoxic activity against the NCI panel of 60 human cancer cell lines (mean IC_{50} = 0.6 μ M), the most sensitive being breast cancer MDA-MB-435 and MDA-N cells (IC_{50} = 0.2 μ M). Another related compound is:



DA-3003-2 [302487]:^{2,3} C₁₅ H₁₆ Cl N₃ O₃

SOURCES – National Cancer Institute, Bethesda, MD (US); University of Pittsburgh, Pittsburgh, PA (US).

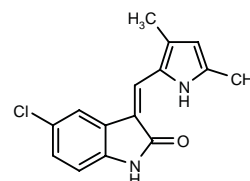
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1. Lazo, J.S. et al. *Discovery and biological evaluation of a new family of potent inhibitors of the dual specificity protein phosphatase Cdc25*. AACR-NCI-EORTC Int Conf Mol Targets Cancer Ther (Oct 29-Nov 2, Miami Beach) 2001, Abst 367.
2. Lazo, J.S. et al. *Discovery and biological evaluation of a new family of potent inhibitors of the dual specificity protein phosphatase Cdc25*. J Med Chem 2001, 44(24): 4042.
3. Southwick, E.C. et al. *Identification of potent Cdc25b2 inhibitors from the National Cancer Institute library*. Proc Amer Assoc Cancer Res 2001, 42: Abst 4463.

SU-5614

311872

(Z)-5-Chloro-3-(3,5-dimethyl-1H-pyrrol-2-ylmethylene)-2,3-dihydro-1H-indol-2-one



C₁₅ H₁₃ Cl N₂ O; Mol wt: 272.7337

ACTION – Tyrosine kinase inhibitor that targets vascular endothelial growth factor receptor 2 (VEGF2; KDR/Flk-1) and platelet-derived growth factor receptor (PDGFR), as well as the related receptor tyrosine kinases Kit and Flt-3. Compound significantly inhibited the proliferation of human acute myeloid leukemia (AML) cell lines expressing wild-type or mutant Flt-3 (EC_{50} = 100 nM), as well as Flt-3 autophosphorylation and phosphorylation of proteins involved in Flt-3 signal transduction. In AML cells expressing mutant Flt-3, compound produced apoptosis with an IC_{50} of 1.0 μ M. In human long-term bone marrow cultures, it induced a concentration-dependent inhibition in the number of stromal fibroblasts (IC_{50} = 123 nM), macrophages and endothelial cells, with a decrease in blood cell production and an increase in fat cells. Potentially useful for the treatment of leukemia and other neoplastic bone marrow diseases.

SOURCE – Sugen (Pharmacia).

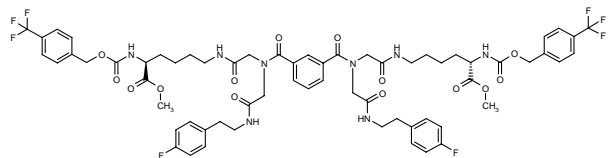
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4. Dührsen, U. et al. *Effects of vascular endothelial and platelet-derived growth factor receptor inhibitors on long-term cultures from normal human bone marrow*. Blood 2000, 96(11, Part 1): Abst 1328.
5. Faber, F. et al. *Growth inhibition of vascular endothelial growth factor (VEGF) producing acute myeloid leukemia cell lines by the VEGF-receptor inhibitor SU5614*. Blood 2001, 98(11, Part 1): Abst 1377.
6. Krystal, G.W. et al. *Indolinone tyrosine kinase inhibitors block kit activation and growth of small cell lung cancer cells*. Cancer Res 2001, 61(9): 3660.
7. Ma, Y. et al. *Indoline derivatives inhibit constitutively activated KIT mutants and kill neoplastic mast cells*. J Invest Dermatol 2000, 114(2): 392.
8. Yee, K.W.H. et al. *SU5416 and SU5614 inhibit wild-type and activated mutant FLT3 signaling in leukemia cells*. Blood 2001, 98(11, Part 1): Abst 3484.

ANGIOGENESIS INHIBITORS

311101

*N^ω, N^{ω'}-[N¹, N³-Bis[*N*-[2-(4-fluorophenyl)ethyl]carbamoylmethyl]benzene-1,3-dicarboxamido]bis(2-oxoethylidene-2,1-diyl)bis(imino)bis[*N*^α-[4-(trifluoromethyl)benzyl-oxycarbonyl]-L-lysine] dimethyl ester*



C64 H70 F8 N8 O14; Mol wt: 1327.2830

ACTION – Angiogenesis and tumor growth inhibitor that acts by specifically binding to the MMP-2 (gelatinase 2) binding site of α_vβ₃ integrin; it exhibited concentration-dependent inhibition of MMP-2 binding to integrin but did not inhibit the binding of vitronectin.

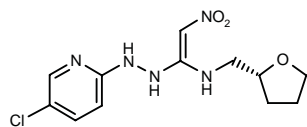
SOURCE – Scripps Research Institute, La Jolla, CA (US).

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1. Boger, D.L. and Cheresch, D.A. (Scripps Research Institute) *Methods for inhibiting angiogenesis and tumor growth*. WO 0172297.

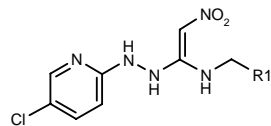
311180

N-[1-[2-(5-Chloropyridin-2-yl)hydrazino]-2-nitrovinyl]-*N*-[tetrahydrofuran-2(*R*)-ylmethyl]amine



C12 H16 Cl N5 O3; Mol wt: 313.7434

ACTION – Matrix metalloproteinase (MMP) inhibitor with an IC₅₀ of 1.1 μM against MMP-9 (gelatinase B). *In vivo*, compound was able to inhibit tumor growth in mice bearing Meth A/AD fibrosarcoma by 52% following i.p. administration at a dose of 50 mg/kg/day for 10 days. In addition, the compound inhibited lung metastasis of colon 26/AD xenografts implanted s.c. in mice at a dose of 50 mg/kg/day i.p. for 11 days. Potentially useful for the treatment of cancer and rheumatoid arthritis, as well as for inhibiting neovascularization and cancer infiltration and metastasis. Other exemplified nitroetheneamines are:



Compound	R1	Formula
311183	1,3-dioxolan-2-yl	C ₁₁ H ₁₄ ClN ₅ O ₄
311184	CH(OMe)2	C ₁₁ H ₁₆ ClN ₅ O ₄
311186	CH2OCH2CH2OH	C ₁₁ H ₁₆ ClN ₅ O ₄

SOURCE – Ishihara Sangyo.

REFERENCES

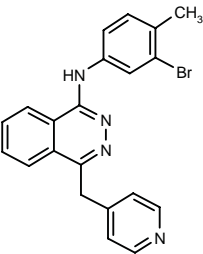
1. Miyata, K. et al. (Ishihara Sangyo Kaisha, Ltd.) *Nitroethenamine derivs. or salts thereof and pharmaceutical compsns. containing the derivs. or the salts*. JP 2001335575, WO 0170696.

NVP-ACC-789

312888

N-(3-Bromo-4-methylphenyl)-4-(pyridin-4-ylmethyl)-phthalazin-1-amine

ACC-789
ZK-202650



C21 H17 Br N4; Mol wt: 405.2973

ACTION – Vascular endothelial growth factor receptor (VEGFR)-2 tyrosine kinase inhibitor (IC₅₀ = 0.02 μM against human enzyme) with 10-20-fold selectivity over VEGFR-1 and VEGFR-3 (IC₅₀ = 0.38 and 0.18 μM, respectively) and inactive against other related tyrosine kinases at up to 10 μM. Compound was found to inhibit VEGF- and basic fibroblast growth factor (bFGF)-induced angiogenesis both *in vitro* and *in vivo*. *In vitro*, it completely inhibited VEGF-induced bovine microvascular endothelial (BME) and bovine aortic endothelial (BAE) cell invasion (IC₅₀ = 0.0055 and 0.016 μM, respectively), as well as bFGF-induced BME and BAE cell invasion (IC₅₀ = 0.035 and 1.102 μM, respectively). In an implant model of angiogenesis in mice, oral doses of 3-100 mg/kg for 6 days blocked in a dose-dependent manner VEGF- and bFGF-induced angiogenesis, with respective ED₅₀ values of 26 and 9 mg/kg.

SOURCES – Novartis; Schering AG.

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1. Bold, G. et al. (Novartis AG) *Phthalazine derivs. for treating inflammatory diseases*. EP 1165085, WO 0059509.

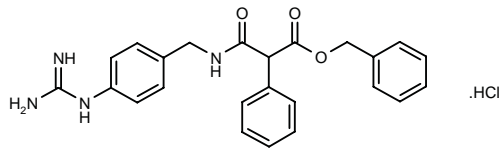
2. Bold, G. et al. *CGP 79787D (PTK787/ZK222584), CGP 84738, NVP-AAC789, NVP-AAD777 and related 1-anilino-(4-pyridylmethyl)phthalazines as inhibitors of VEGF- and bFGF-induced angiogenesis*. Drugs Fut 2002, 027(01): 0043.

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ST-401

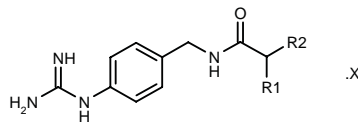
310526

2-[N-(4-Guanidinobenzyl)carbamoyl]-2-phenylacetic acid benzyl ester hydrochloride



C24 H24 N4 O3 . HCl; Mol wt: 452.9395

ACTION – A selective inhibitor of urokinase-type plasminogen activator (uPA) that gave a K_i value of 1.4 μ M for uPA inhibition versus K_i values of > 1000 μ M against plasmin, factor Xa and thrombin. Potentially useful for the treatment of cancer. Other exemplified guanidino-containing compounds are:



Compound	R1	R2	X	Formula
ST-390 [310527]	CH2OH	Ph	HCl	C ₁₇ H ₂₀ N ₄ O ₂ ·HCl
ST-406 [310528]	CO2H	Ph	HCl	C ₁₇ H ₁₈ N ₄ O ₃ ·HCl
ST-100 [310529]	CO2CH2Ph	1-adamantyl		C ₂₈ H ₃₄ N ₄ O ₃

SOURCES – Max-Planck-Gesellschaft, München (DE); Wiley.

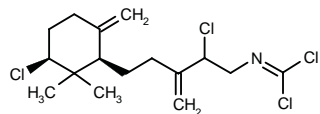
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OTHER ONCOLYTIC DRUGS

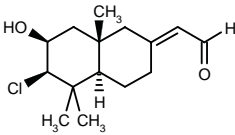
310718

(+)-N-[2-Chloro-5-[3(*S*)-chloro-2,2-dimethyl-6-methylenecyclohexyl]-3-methylenepent-1(*R*)-yl]-N-(dichloromethylene)amine

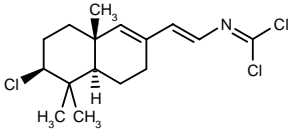


C16 H23 Cl4 N; Mol wt: 371.1767

ACTION – Antitumor compound isolated from the marine sponge *Stylotella aurantium*. *In vitro*, this compound displayed IC₅₀ values of 1 μ g/ml against leukemia P388 cells and 0.1 μ g/ml against the human lung carcinoma A549, human colon adenocarcinoma HT-29 and human melanoma MEL-28. Other compounds from the same source are:



Compound	Isomer	Formula
310719	(+)-E	C ₁₅ H ₂₃ ClO ₂
310720	(-)-Z	C ₁₅ H ₂₃ ClO ₂



310721: C16 H22 Cl3 N

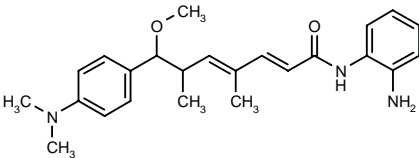
SOURCE – PharmaMar.

REFERENCES

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310755

N-(2-Aminophenyl)-7-[4-(dimethylamino)phenyl]-7-methoxy-4,6-dimethyl-2,4-heptadienamide



C24 H31 N3 O2; Mol wt: 393.5279

ACTION – Histone deacetylase (HDAC) inhibitor with an IC₅₀ of 7 μ M against human recombinant HDAC-1, proven to inhibit histone H4 acetylation in human bladder cancer T24 cells with an EC₅₀ of 5 μ M. *In vivo*, compound produced significant inhibition of human lung cancer A549 xenografts in mice. Potentially useful in the treatment of proliferative diseases.

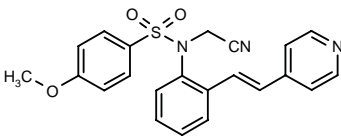
SOURCE – MethylGene.

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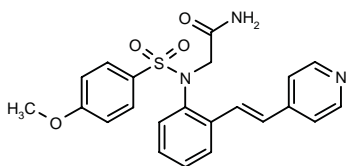
311128

N-(Cyanomethyl)-4-methoxy-N-[2-[2-(4-pyridyl)vinyl]-phenyl]benzenesulfonamide



C22 H19 N3 O3 S; Mol wt: 405.4761

ACTION – Antitumor agent reported to inhibit the proliferation of human colorectal cancer KM12-HX cells. Another exemplified sulfonamide derivative is:



311129: C22 H21 N3 O4 S

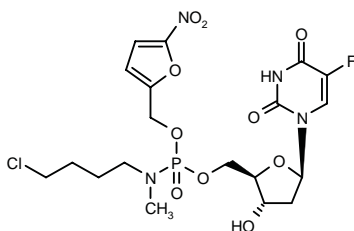
SOURCE – Sankyo.

REFERENCES

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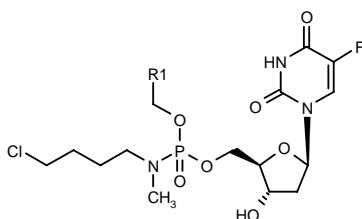
311618^{1,2}

5'-O-[[N-(4-Chlorobutyl)-N-methylamino](5-nitrofuran-2-ylmethoxy)phosphoryl]-2'-deoxy- 5-fluorouridine



C19 H25 Cl F N4 O10 P; Mol wt: 554.8495

ACTION – Phosphoramidate prodrug for intracellular delivery, useful for the treatment of cancer. Compound gave an IC₅₀ of 2.3 nM when incubated for 48 h with L1210 leukemia cells, comparable to the IC₅₀ of 0.64 nM displayed by the active compound. It demonstrated better activity than the parent drug (IC₅₀ = 1280 nM vs. 3670 nM) against thymidine kinase-deficient (TK-) LM cells. Other exemplified compounds are:



Compound	R1	Formula
311619 ^{1,2}	1,4-dioxo-1,4-dihydro-2-Naph	C ₂₆ H ₂₈ ClFN ₃ O ₉ P
311620 ¹	5-MeO-1-Me-4,7-dioxo-4,7-dihydro-2-indolyl	C ₂₅ H ₃₁ ClFN ₄ O ₁₀ P

SOURCE – Purdue Research Foundation, West Lafayette, IN (US).

REFERENCES

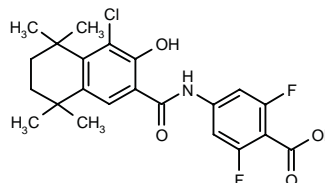
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AGN-195183

310482

4-(4-Chloro-3-hydroxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-ylcarboxamido)-2,6-difluorobenzoic acid



C22 H22 Cl F2 N O4; Mol wt: 437.8678

ACTION – Retinoic acid receptor RAR α -selective agonist with antitumor activity against breast cancer and leukemia cells *in vitro* and *in vivo*, and less skin toxicity compared to nonselective RAR α agonists. A phase I study in patients with advanced malignancies showed dose-limiting toxicity at a dose of 60 mg/m²/day; pharmacokinetic analysis demonstrated rapid absorption, with a t_{max} of 1 h and a terminal elimination half-life of 4.17 h. No significant toxicity was seen with a lower dose of 30 mg/m²/day and patient accrual at this dose continues.

SOURCE – Allergan.

REFERENCES

1. Nehme, A. et al. (Allergan, Inc.) *Treatment of tumors with RAR α selective retinoid cpds. in combination with other anti-tumor agents.* WO 0174759.

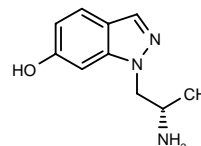
2. Taylor, C. et al. *A phase I and pharmacokinetic clinical trial of the orally administered retinoic acid receptor- α agonist, AGN-195183.* AACR-NCI-EORTC Int Conf Mol Targets Cancer Ther (Oct 29-Nov 2, Miami Beach) 2001, Abst 298.

3. Wang, Q. et al. *1,25-Dihydroxyvitamin D3 and retinoic acid analogues induce differentiation in breast cancer cells with function- and cell-specific additive effects.* Breast Cancer Res Treat 2001, 67(2): 157.

OCULAR MEDICATIONS

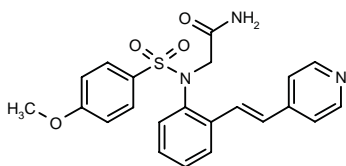
310944

(+)-1-[2(S)-Aminopropyl]-1H-indazol-6-ol



C10 H13 N3 O; Mol wt: 191.2327

ACTION – Antiglaucoma agent, a 5-HT₂ receptor agonist found to produce a significant decrease in intraocular pressure in lasered eyes of cynomolgus monkeys when administered at 300 μ g by topical application.



311129: C22 H21 N3 O4 S

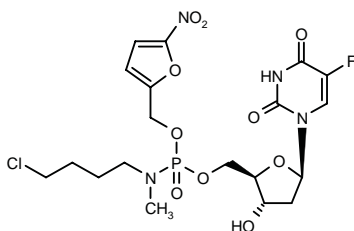
SOURCE – Sankyo.

REFERENCES

1. Shibata, T. et al. (Sankyo Co., Ltd.) *Sulfonamide derivs.* JP 2001261649.

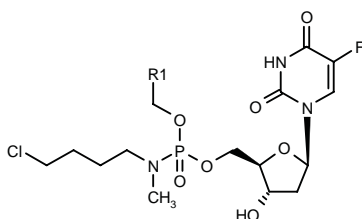
311618^{1,2}

5'-O-[[N-(4-Chlorobutyl)-N-methylamino](5-nitrofuran-2-ylmethoxy)phosphoryl]-2'-deoxy- 5-fluorouridine



C19 H25 Cl F N4 O10 P; Mol wt: 554.8495

ACTION – Phosphoramidate prodrug for intracellular delivery, useful for the treatment of cancer. Compound gave an IC₅₀ of 2.3 nM when incubated for 48 h with L1210 leukemia cells, comparable to the IC₅₀ of 0.64 nM displayed by the active compound. It demonstrated better activity than the parent drug (IC₅₀ = 1280 nM vs. 3670 nM) against thymidine kinase-deficient (TK-) LM cells. Other exemplified compounds are:



Compound	R1	Formula
311619 ^{1,2}	1,4-dioxo-1,4-dihydro-2-Naph	C ₂₆ H ₂₈ ClFN ₃ O ₉ P
311620 ¹	5-MeO-1-Me-4,7-dioxo-4,7-dihydro-2-indolyl	C ₂₅ H ₃₁ ClFN ₄ O ₁₀ P

SOURCE – Purdue Research Foundation, West Lafayette, IN (US).

REFERENCES

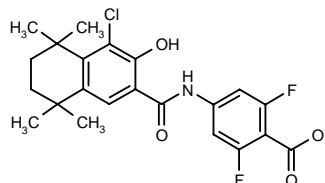
1. Borch, R.F. et al. (Purdue Research Foundation) *Phosphoramidate prodrugs.* WO 0174827.

2. Tobias, S.C. and Borch, R.F. *Synthesis and biological studies of novel nucleoside phosphoramidate prodrugs.* J Med Chem 2001, 44(25): 4475.

AGN-195183

310482

4-(4-Chloro-3-hydroxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-ylcarboxamido)-2,6-difluorobenzoic acid



C22 H22 Cl F2 N O4; Mol wt: 437.8678

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SOURCE – Allergan.

REFERENCES

1. Nehme, A. et al. (Allergan, Inc.) *Treatment of tumors with RAR α selective retinoid cpds. in combination with other anti-tumor agents.* WO 0174759.

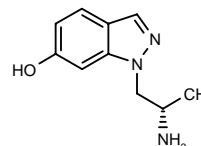
2. Taylor, C. et al. *A phase I and pharmacokinetic clinical trial of the orally administered retinoic acid receptor- α agonist, AGN-195183.* AACR-NCI-EORTC Int Conf Mol Targets Cancer Ther (Oct 29-Nov 2, Miami Beach) 2001, Abst 298.

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OCULAR MEDICATIONS

310944

(+)-1-[2(S)-Aminopropyl]-1H-indazol-6-ol



C10 H13 N3 O; Mol wt: 191.2327

ACTION – Antiglaucoma agent, a 5-HT₂ receptor agonist found to produce a significant decrease in intraocular pressure in lasered eyes of cynomolgus monkeys when administered at 300 μ g by topical application.

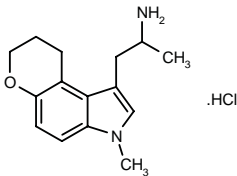
SOURCES – Alcon; Yamanouchi.

REFERENCES

1. May, J.A. and Dantanarayana, A.P. (Alcon Universal, Ltd.; Yamanouchi Pharmaceutical Co., Ltd.) *5HT2 agonists for controlling IOP and treating glaucoma*. WO 0170207.

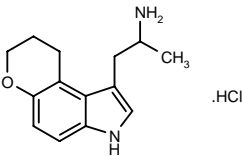
310946

1-(3-Methyl-3,7,8,9-tetrahydropyrano[3,2-*e*]indol-1-yl)-propan-2-amine hydrochloride



C15 H20 N2 O . HCl; Mol wt: 280.7969

ACTION – Antiglaucoma agent, a 5-HT₂ receptor agonist with high affinity for the receptor (IC₅₀ = 0.82 nM). In functional assays, it demonstrated agonist activity (EC₅₀ = 189 nM) and high efficacy (E_{max} = 119%). Compound caused a significant decrease in intraocular pressure in lasered eyes of cynomolgus monkeys when administered at 300 µg by topical application. Another exemplified pyranoinndole is:



310947: C14 H18 N2 O . HCl

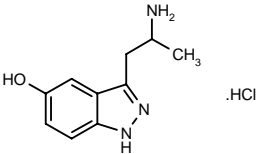
SOURCE – Alcon.

REFERENCES

1. May, J.A. and Chen, H.-H. (Alcon Universal, Ltd.) *Pyranoinndoles for treating glaucoma*. WO 0170745.

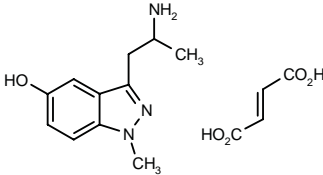
310948

3-(2-Aminopropyl)-1*H*-indazol-5-ol hydrochloride



C10 H13 N3 O . HCl; Mol wt: 227.6936

ACTION – Antiglaucoma agent, a 5-HT₂ receptor agonist with high affinity for the receptor (IC₅₀ = 2.5 nM). In functional assays, it demonstrated agonist activity (EC₅₀ = 1.2 µM) and high efficacy (E_{max} = 97%). Another exemplified 5-hydroxyindazole derivative is:



310968: C11 H15 N3 O . C4 H4 O4

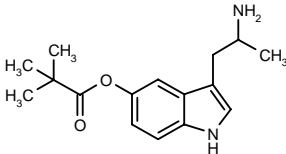
SOURCE – Alcon.

REFERENCES

1. May, J.A. and Feng, Z. (Alcon Universal, Ltd.) *5-Hydroxy indazole derivs. for treating glaucoma*. WO 0170701.

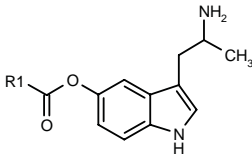
310949

2,2-Dimethylpropionic acid 3-(2-aminopropyl)-1*H*-indol-5-yl ester



C16 H22 N2 O2; Mol wt: 274.3618

ACTION – Antiglaucoma agent, a 5-HT₂ receptor agonist with the advantage of increased stability compared to α-methylserotonin, as demonstrated by decreased degradation under experimental stress conditions. Other exemplified 5-hydroxyindole derivatives are:



Compound	R1	Formula
310950	i-Pr	C ₁₅ H ₂₀ N ₂ O ₂
310951	cyclopropyl	C ₁₅ H ₁₈ N ₂ O ₂

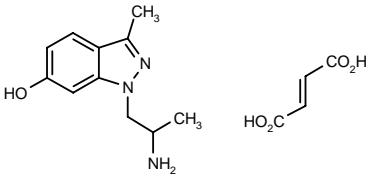
SOURCE – Alcon.

REFERENCES

1. May, J.A. and Zinke, P.W. (Alcon Universal, Ltd.) *5-Hydroxy indole derivs. for treating glaucoma*. WO 0170686.

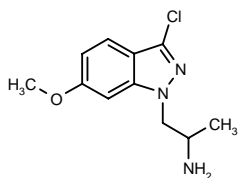
310952

1-(2-Aminopropyl)-3-methyl-1*H*-indazol-6-ol fumarate



C11 H15 N3 O . C4 H4 O4; Mol wt: 321.3311

ACTION – Antiglaucoma agent, a 5-HT₂ receptor agonist with high affinity for the receptor (IC₅₀ = 3.0 nM). In functional assays, it demonstrated agonist activity (EC₅₀ = 483 nM) and high efficacy (E_{max} = 87%). Another exemplified 6-hydroxyindazole derivative is:



310953: C11 H14 Cl N3 O

SOURCE – Alcon.

REFERENCES

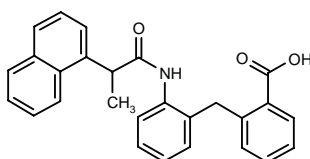
1. May, J.A. et al. (Alcon Universal, Ltd.) 6-Hydroxy-indazole derivs. for treating glaucoma. WO 0170702.

METABOLIC DRUGS

TREATMENT OF BONE DISEASES

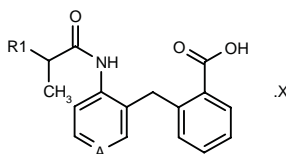
310678

2-[2-[2-(1-Naphthyl)propionamido]benzyl]benzoic acid



C27 H23 N O3; Mol wt: 409.4827

ACTION – Agent with high affinity for the prostaglandin E₂ (PGE₂) receptor, particularly the EP₄ receptor subtype (K_i = 0.0027 μM against EP₄ receptors in CHO cell membranes), proven to inhibit PGE₂-induced production of cAMP with an IC₅₀ of 0.01 μM. Potentially useful for the treatment of bone diseases, cancer, systemic granuloma, immune disorders, allergy, atopy, asthma, alveolar abscess, gingivitis, periodontitis, neuronal death, Alzheimer's disease, lung and liver disorders, nephritis, renal insufficiency, myocardial ischemia, Kawasaki's disease, burns, ulcerative colitis and Crohn's disease, as well as in the treatment of sleep and platelet aggregation disorders. Other exemplified benzoic acid derivatives include the following:



Compound	R1	A	X	Formula
310679	1-Naph	N	HCl	C ₂₆ H ₂₂ N ₂ O ₃ ·HCl
310680	4-(PhCH ₂ O)-Ph	CH		C ₃₀ H ₂₇ NO ₄

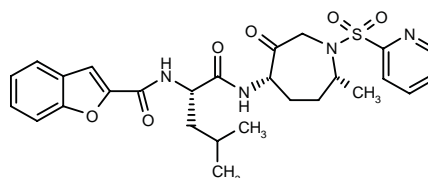
SOURCE – Ono.

REFERENCES

1. Tani, K. et al. (Ono Pharmaceutical Co., Ltd.) Benzoic acid derivs., process for producing the same and drugs containing the same as the active ingredient. WO 0162708.

310712

N²-(1-Benzofuran-2-ylcarbonyl)-N¹-[7(R)-methyl-3-oxo-1-(2-pyridinylsulfonyl)perhydroazepin-4(S)-yl]-L-leucinamide



C27 H32 N4 O6 S; Mol wt: 540.6378

ACTION – Cathepsin K inhibitor, a specifically claimed 4-aminoazepan-3-one derivative, potentially useful for the treatment of osteoporosis, periodontitis, gingivitis, osteoarthritis, rheumatoid arthritis and parasitic infections, particularly malaria.

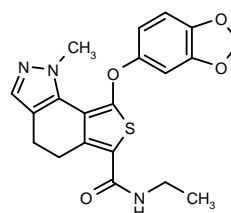
SOURCE – GlaxoSmithKline.

REFERENCES

1. Cummings, M.D. et al. (SmithKline Beecham Corp.) Protease inhibitors. WO 0170232.

311589

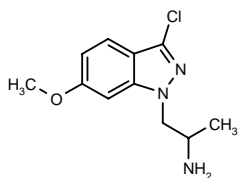
8-(1,3-Benzodioxol-5-yloxy)-N-ethyl-1-methyl-4,5-dihydro-1H-thieno[3,4-g]indazole-6-carboxamide



C20 H19 N3 O4 S; Mol wt: 397.4531

ACTION – Agent with the ability to promote osteogenesis, potentially useful for the treatment and prevention of bone and articular diseases including osteoporosis. Compound was found to induce alkaline phosphatase activity in interstitial cells from the bone marrow of rat femur and enhanced the expression of chondromodulin-I (ChM-I), as demonstrated by an increase in ChM-I mRNA levels in ATDC5 cells. Other exemplified fused heterocyclic compounds are:

ACTION – Antiglaucoma agent, a 5-HT₂ receptor agonist with high affinity for the receptor (IC₅₀ = 3.0 nM). In functional assays, it demonstrated agonist activity (EC₅₀ = 483 nM) and high efficacy (E_{max} = 87%). Another exemplified 6-hydroxyindazole derivative is:



310953: C11 H14 Cl N3 O

SOURCE – Alcon.

REFERENCES

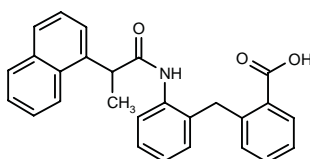
1. May, J.A. et al. (Alcon Universal, Ltd.) 6-Hydroxy-indazole derivs. for treating glaucoma. WO 0170702.

METABOLIC DRUGS

TREATMENT OF BONE DISEASES

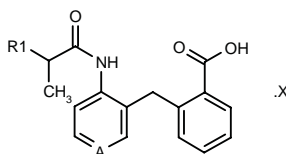
310678

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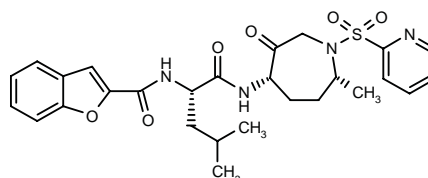
SOURCE – Ono.

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310712

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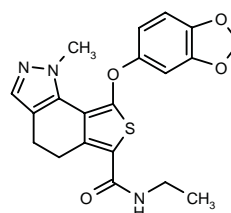
SOURCE – GlaxoSmithKline.

REFERENCES

1. Cummings, M.D. et al. (SmithKline Beecham Corp.) Protease inhibitors. WO 0170232.

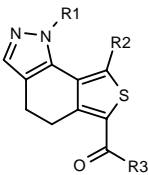
311589

8-(1,3-Benzodioxol-5-yloxy)-N-ethyl-1-methyl-4,5-dihydro-1H-thieno[3,4-g]indazole-6-carboxamide

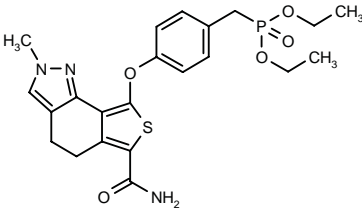


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Compound	R1	R2	R3	Formula
311590	Me	SO2Pr	NH2	C ₁₄ H ₁₇ N ₃ O ₃ S ₂
311591	H	OPh	NH2	C ₁₆ H ₁₃ N ₃ O ₂ S
311592	Me	1,3-benzodioxol-5-yl-O	NH2	C ₁₈ H ₁₅ N ₃ O ₄ S
311593	Me	4-(PhCH2O)-PhO	NH2	C ₂₄ H ₂₁ N ₃ O ₃ S
311594	Me	4-[PO(OEt)2CH2]-PhO	NH2	C ₂₂ H ₂₆ N ₃ O ₅ PS
311596	Me	4-CF3-PhO	NH2	C ₁₈ H ₁₄ F ₃ N ₃ O ₂ S
311597	Me	1,3-benzodioxol-5-yl-O	Me	C ₁₉ H ₁₆ N ₂ O ₄ S



311595: C22 H26 N3 O5 P S

SOURCE – Takeda.

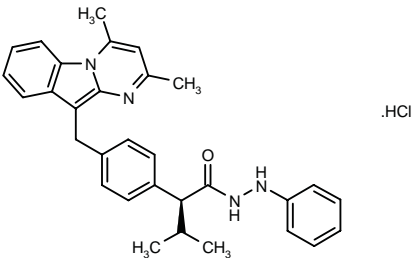
REFERENCES

1. Yasuma, T. et al. (Takeda Chemical Industries, Ltd.) *Fused heterocyclic derivs., their production and use.* WO 0174823.

TREATMENT OF LIPOPROTEIN DISORDERS

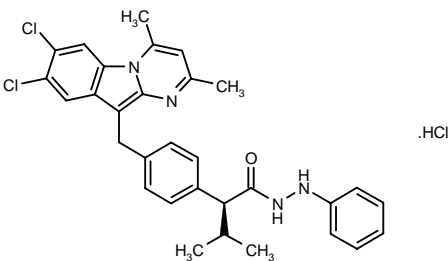
311464

2(S)-[4-(2,4-Dimethylpyrimido[1,2-*a*]indol-10-ylmethyl)-phenyl]-3-methyl-*N*-phenylbutyrylhydrazide hydrochloride



C31 H32 N4 O . HCl; Mol wt: 513.0817

ACTION – Agent with the ability to inhibit apolipoprotein B (apo B)-associated lipoprotein secretion, as demonstrated in HepG2 cells (IC₅₀ = 6.6 nM). *In vivo*, compound was shown to lower plasma non-HDL cholesterol levels in both high-fat-fed rats and LDL receptor-defective mice with ED₅₀ values of 0.17 and 0.26 mg/kg p.o., respectively. Potentially useful for the treatment of hyperlipidemia, atherosclerosis, obesity and pancreatitis. Another exemplified hydrazide derivative is:



311465: C31 H30 Cl2 N4 O . HCl

SOURCE – Yamanouchi.

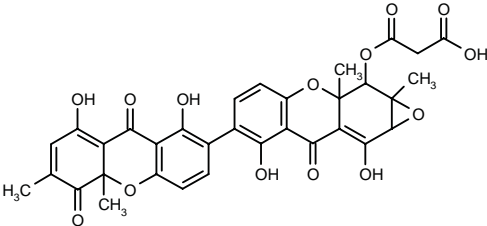
REFERENCES

1. Suga, A. et al. (Yamanouchi Pharmaceutical Co., Ltd.) *Hydrazide derivs.* WO 0174817.

BE-063437A

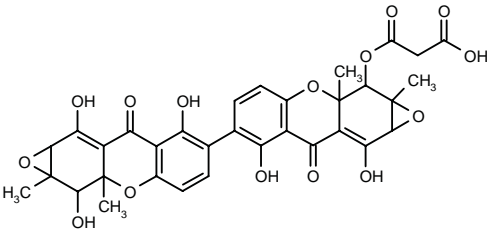
311484

Malonic acid 6-(1,8-dihydroxy-3,4a-dimethyl-4,9-dioxo-4a,9-dihydro-4*H*-xanthen-7-yl)-7,9-dihydroxy-1a,2a-dimethyl-8-oxo-2,2a,8,9a-tetrahydro-1a*H*-oxireno[*b*]-xanthen-2-yl monoester



C33 H26 O14; Mol wt: 646.5544

ACTION – Agent for the treatment of hyperlipidemia, an inhibitor of adenosine triphosphate (ATP)-citrate lyase (50% inhibition at 4.0 µg/ml in rat liver). Another exemplified compound is:



BE-063437B [311485]: C33 H28 O15

SOURCE – Banyu.

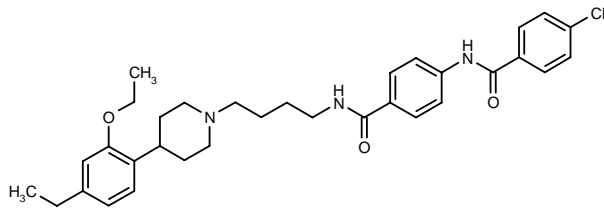
REFERENCES

1. Hirano, A. et al. (Banyu Pharmaceutical Co., Ltd.) *ATP-citrate lyase inhibitor BE-063437 and its preparation method.* JP 2001261682.

GW-532^{1,2}

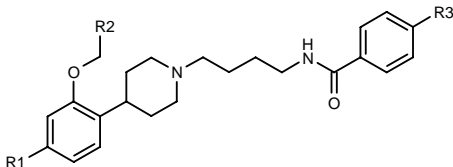
313070

4-Chloro-*N*-[4-[*N*-[4-(2-ethoxy-4-ethylphenyl)piperidin-1-yl]butyl]carbamoyl]phenyl]benzamide

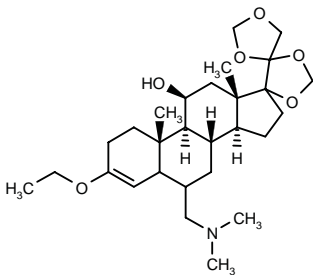


C33 H40 Cl N3 O3; Mol wt: 562.1500

ACTION – Lipid-lowering agent that acts by upregulating the expression of LDL receptors via an interaction with the SREBP (sterol regulatory element-binding protein)–SCAP (cleavage-activating protein) complex. Compound specifically binds to SCAP, presumably in the putative sterol-sensing domain, and increases the mature nuclear form of SREBPs, which activate gene expression. When administered to hamsters given a high-fat diet, a dose of 5 mg/kg p.o. reduced both LDL cholesterol and triglyceride levels by 64%, whereas HDL cholesterol was not significantly affected (+ 17%). Other related compounds are:



Compound	R1	R2	R3	Formula
GW-300 [313079] ²	OEt	Me	4-Cl-PhCONH	C ₃₃ H ₄₀ ClN ₃ O ₄
GW-575 [313080] ^{1,2}	i-Pr	H	COPh	C ₃₃ H ₄₀ N ₂ O ₃



GW-707² [313078]: C28 H45 N O6

SOURCE – GlaxoSmithKline.

REFERENCES

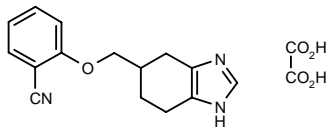
1. Grand-Perret, T.A.R. and Issandou, M. (Glaxo Group Ltd.) *Binding competition of SREBP-cleavage activating protein (SCAP) antagonists*. WO 0106261.

2. Grand-Perret, T. et al. *SCAP ligands are potent new lipid-lowering drugs*. Nat Med 2001, 7(12): 1332.

TREATMENT OF OBESITY
AND NUTRITIONAL DISORDERS

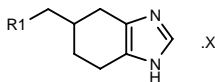
310425

2-(4,5,6,7-Tetrahydro-1*H*-benzimidazol-5-ylmethoxy)-benzonitrile oxalate

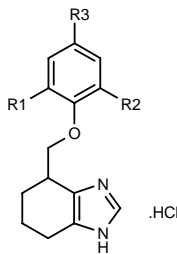


C15 H15 N3 O . C2 H2 O4; Mol wt: 343.3373

ACTION – Agent with affinity for the histamine H₃ receptor, expected to be useful for the treatment of histamine H₃ receptor-mediated conditions such as obesity, bulimia, binge eating, anorexia, impaired glucose tolerance, type 2 diabetes, allergic rhinitis and ulcers. Other exemplified condensed imidazoles include the following:



Compound	R1	X	Formula
310426	1,3-benzodioxol-5-yl-O	oxalate	C ₁₅ H ₁₆ N ₂ O ₃ ·C ₂ H ₂ O ₄
310427	2,6-(F)-2-PhO	HCl	C ₁₄ H ₁₄ F ₂ N ₂ O·HCl
310428	2,4-(Cl)2-PhOCH2	HCl	C ₁₅ H ₁₆ Cl ₂ N ₂ O·HCl
310429	4-CF3-PhCH2O		C ₁₆ H ₁₇ F ₃ N ₂ O
310430	3-CF3-2-Cl-PhCH2O		C ₁₆ H ₁₆ ClF ₃ N ₂ O



Compound	R1	R2	R3	Formula
310431	Me	Me	CN	C ₁₇ H ₁₉ N ₃ O·HCl
310432	PhCO	H	Cl	C ₂₁ H ₁₉ ClN ₂ O ₂ ·HCl

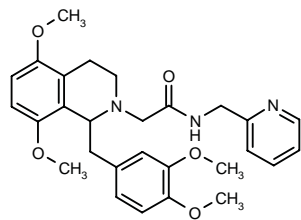
SOURCES – Boehringer Ingelheim Novo Nordisk.

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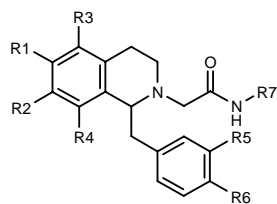
310445

2-[1-(3,4-Dimethoxybenzyl)-5,8-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl]-N-(pyridin-2-ylmethyl)acetamide



C28 H33 N3 O5; Mol wt: 491.5847

ACTION – Orexin OX1 receptor antagonist, potentially useful for the treatment of obesity and sleep disorders. Other specifically claimed 1,2,3,4-tetrahydroisoquinolinyl-substituted acetamides include the following:



Compound	R1	R2	R3	R4	R5=R6	R7	Formula
310447	H	H	OMe	OPr	OMe	2-Pyr-CH2	C ₃₀ H ₃₇ N ₃ O ₅
310448	OMe	OMe	H	H	OMe	1-indanyl	C ₃₁ H ₃₈ N ₂ O ₅
310449	OMe	i-PrO	H	H	OMe	6-Me-1-indanyl	C ₃₄ H ₄₂ N ₂ O ₅
310450	OMe	OCOn(Me)2	H	H	OMe	1-indanyl	C ₃₃ H ₃₉ N ₃ O ₆
310452	OMe	OEt	H	H	OMe	1-indanyl	C ₃₂ H ₃₈ N ₂ O ₅
310453	OMe	i-PrO	H	H	OMe	CH2Ph	C ₃₁ H ₃₈ N ₂ O ₅
310454	OMe	OMe	H	H	Me	1(S)-indanyl	C ₃₁ H ₃₈ N ₂ O ₃
310456	OMe	OMe	H	H	Cl	3-Pyr-CH2	C ₂₆ H ₂₇ Cl ₂ N ₃ O ₃

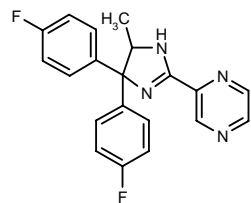
SOURCE – Actelion.

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310672

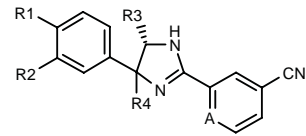
2-[4,4-Bis(4-fluorophenyl)-5-methyl-4,5-dihydro-1H-imidazol-2-yl]pyrazine



C20 H16 F2 N4; Mol wt: 350.3704

ACTION – Neuropeptide Y (NPY) Y₅ antagonist with an IC₅₀ of 3.4 nM for inhibition of [¹²⁵I]-peptide YY binding to Y₅ receptors. It showed good pharmacokinetic parameters when administered p.o. or i.v. to rats. Potentially useful for the treatment of hypertension, kidney and cardiac diseases, arteriosclerosis, hyperphagia, depression, anxiety, epilepsy, dementia, pain, alcohol and drug abuse, obesity, diabetes, hypercholesterolemia and

hyperlipidemia, sexual dysfunction, enterokinetic disorders, respiratory diseases, inflammation and glaucoma. Other exemplified imidazoline derivatives include the following:



Compound	R1	R2	R3	R4	A	Formula
310673	H	F	H	3-F-Ph	CH	C ₂₂ H ₁₅ F ₂ N ₃
310674	F	H	Me	6-F-3-Pyr	N	C ₂₁ H ₁₅ F ₂ N ₅

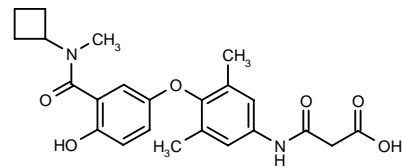
SOURCE – Banyu.

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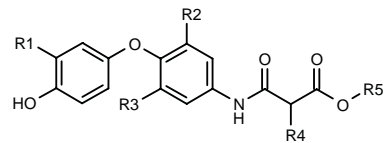
311149

N-[4-[3-(N-Cyclobutyl-N-methylcarbamoyl)-4-hydroxy-phenoxy]-3,5-dimethylphenyl]malonic acid



C23 H26 N2 O6; Mol wt: 426.4664

ACTION – Thyroid receptor ligand with the ability to increase energy expenditure. As such, it is expected to be useful for the treatment of obesity and diabetes, as well as other thyroid hormone-mediated conditions such as hyperlipidemia and hypercholesterolemia, glaucoma, cardiac arrhythmia, skin disorders, hypothyroidism, thyroid cancer, atherosclerosis, hypertension, coronary heart disease, congestive heart failure, depression, osteoporosis and hair loss. Other specifically claimed compounds are:



Compound	R1	R2	R3	R4	R5	Formula
311152	cyclopropyl-CH2SO2	Cl	Cl	H	H	C ₁₉ H ₁₇ Cl ₂ NO ₇ S
311153	cyclobutyl-CH2SO2	Me	Me	Me	H	C ₂₃ H ₂₇ NO ₇ S
311154	cyclohexyl-CH2SO2	Me	Me	H	H	C ₂₄ H ₂₉ NO ₇ S
311155	4-F-PhCH(OH)	Me	Me	H	H	C ₂₄ H ₂₂ FNO ₆
311156	cyclobutyl-CH2SO2	Me	Me	H	Et	C ₂₄ H ₂₉ NO ₇ S
311157	4-F-PhSO2	Me	Cl	H	H	C ₂₂ H ₁₇ ClFNO ₇ S
311158	4-F-PhSO2	Me	Me	Me	Me	C ₂₅ H ₂₄ FNO ₇ S
311159	4-F-PhSO2	Cl	Cl	Me	H	C ₂₂ H ₁₆ Cl ₂ FNO ₇ S

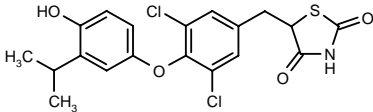
SOURCE – Pfizer.

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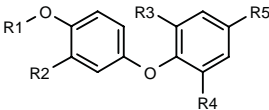
311422

5-[3,5-Dichloro-4-(4-hydroxy-3-isopropylphenoxy)-benzyl]thiazolidine-2,4-dione



C19 H17 Cl2 N O4 S; Mol wt: 426.3183

ACTION – Thyroid receptor ligand, expected to be useful for the treatment of thyroid hormone-mediated conditions including hyperlipidemia, glaucoma, cardiac arrhythmias, skin disorders, hypothyroidism, thyroid cancer, atherosclerosis, hypertension, congestive heart failure, depression and osteoporosis. Preferably, compound is used in the treatment of obesity and diabetes. Other exemplified compounds are:



Compound	R1	R2	R3=R4	R5	Formula
311423	H	i-Pr	Me	2,4-dioxo-5-thiazolidinylidene=CH	C ₂₁ H ₂₁ NO ₄ S
311424	H	i-Pr	Me	2,4-dioxo-5-thiazolidinyl-CH2	C ₂₁ H ₂₃ NO ₄ S
311425	H	cyclopropyl-NHSO2	Cl	2,4-dioxo-5-thiazolidinyl-CH2	C ₁₉ H ₁₆ Cl ₂ N ₂ O ₆ S ₂
311431	H	cyclobutyl-N(Me)CO	Cl	2,4-dioxo-5-thiazolidinyl-CH2	C ₂₂ H ₂₀ Cl ₂ N ₂ O ₅ S
311432	H	i-Pr	Cl	3,5-dioxo-1,2,4-oxadiazolidin-2-yl-CH2	C ₁₈ H ₁₆ Cl ₂ N ₂ O ₅
311433	Me	i-Pr	Me	3,5-dioxo-1,2,4-oxadiazolidin-2-yl-CH2	C ₂₁ H ₂₄ N ₂ O ₅
311434	H	i-Pr	Me	3,5-dioxo-1,2,4-oxadiazolidin-2-yl-CH2	C ₂₀ H ₂₂ N ₂ O ₅
311435	H	i-Pr	Me	5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl	C ₁₉ H ₂₁ N ₃ O ₃

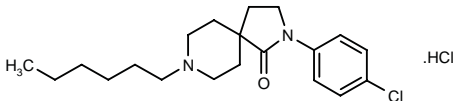
SOURCE – Pfizer.

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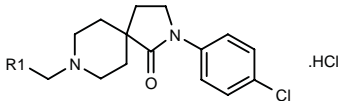
311497

2-(4-Chlorophenyl)-8-hexyl-2,8-diazaspiro[4.5]decan-1-one hydrochloride



C20 H29 Cl N2 O . HCl; Mol wt: 385.3760

ACTION – Agent with affinity for σ receptors that was shown to bind to σ_1 receptors in guinea pig brain preparations. *In vivo*, it inhibited food intake by 99.7 and 88.4%, respectively, following i.p. and p.o. administration at 30 mg/kg in rats. In a rat acute toxicity test, no deaths were observed when this compound was given at a dose of 300 mg/kg p.o. Potentially useful as an antiobesity agent. Other exemplified pyrrolidinone derivatives include the following:



Compound	R1	Formula
311499	Pr	C ₁₈ H ₂₅ ClN ₂ O.HCl
311500	Bu	C ₁₉ H ₂₇ ClN ₂ O.HCl
311501	t-Bu	C ₁₉ H ₂₇ ClN ₂ O.HCl
311502	cyclopropyl	C ₁₈ H ₂₃ ClN ₂ O.HCl
311503	CH2Ph	C ₂₂ H ₂₅ ClN ₂ O.HCl
311504	CH2SMe	C ₁₇ H ₂₃ ClN ₂ OS.HCl

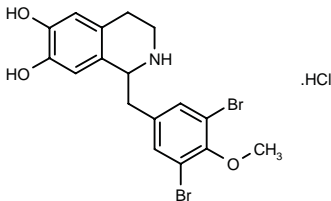
SOURCE – Mitsui Chemicals.

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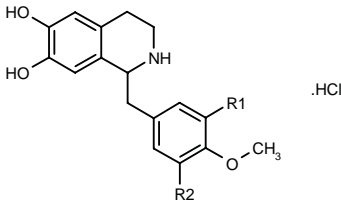
311547

1-(3,5-Dibromo-4-methoxybenzyl)-1,2,3,4-tetrahydro-isoquinoline-6,7-diol hydrochloride



C17 H17 Br2 N O3 . HCl; Mol wt: 479.5942

ACTION – β_3 -Adrenoceptor agonist that modulates fat metabolism in adipose tissues and is potentially useful for the treatment of obesity and disorders related therewith. Other exemplified benzyl-substituted isoquinolines are:



Compound	R1=R2	Isomer	Formula
311548	Br	S	C ₁₇ H ₁₇ Br ₂ NO ₃ .HCl
311549	Br	R	C ₁₇ H ₁₇ Br ₂ NO ₃ .HCl
311550	Cl		C ₁₇ H ₁₇ Cl ₂ NO ₃ .HCl
311551	Cl	S	C ₁₇ H ₁₇ Cl ₂ NO ₃ .HCl
311552	Cl	R	C ₁₇ H ₁₇ Cl ₂ NO ₃ .HCl

SOURCE – Molecular Design International.

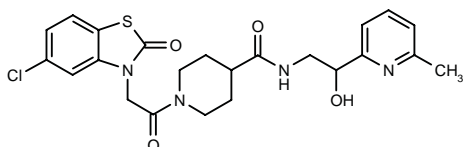
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FR-235208

311253

1-[2-(5-Chloro-2,3-dihydro-2-oxobenzothiazol-3-yl)acetyl]-N-[2-hydroxy-2-(6-methylpyridin-2-yl)ethyl]piperidine-4-carboxamide



C23 H25 Cl N4 O4 S; Mol wt: 488.9935

ACTION – Neuropeptide Y (NPY) Y_5 receptor antagonist with nanomolar affinity for the receptor (IC_{50} = 3.3 nM), potentially useful for the treatment of obesity.

SOURCE – Fujisawa.

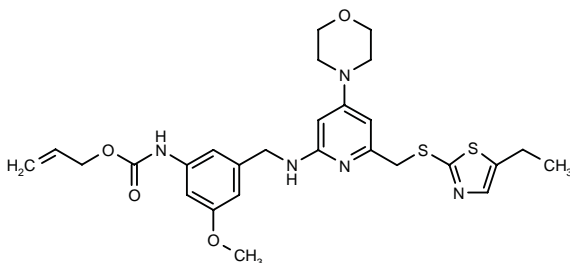
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J-104870

311264

N-[3-[6-(5-Ethylthiazol-2-yl)sulfanylmethyl]-4-(4-morpholin-yl)pyridin-2-ylaminomethyl]-5-methoxyphenyl]carbamic acid allyl ester



C27 H33 N5 O4 S2; Mol wt: 555.7207

ACTION – High-affinity neuropeptide Y (NPY) Y_1 receptor ligand (K_i = 0.26 and 0.51 nM for human and rat receptors, respectively) with high selectivity over human Y_2 , Y_4 and Y_6 receptors (K_i = > 6000 nM) and *in vitro* functional antagonist activity (IC_{50} = 3.2 nM for inhibition of NPY-induced Ca^{2+} increase in CHO cells expressing human Y_1 receptors). *In vivo*, the intracerebroventricular (i.c.v.) administration of compound at a dose of 200 μ g significantly suppressed NPY-induced feeding in satiated rats, and both i.c.v (200 μ g) and oral (100 mg/kg) doses significantly suppressed spontaneous food intake for 24 h by 25 and 18%, respectively, in Zucker fatty rats. Potentially useful for the treatment of obesity.

SOURCE – Banyu.

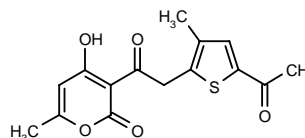
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HEMATINIC AGENTS AND HEMATOPOIETIC GROWTH FACTORS

311437

3-[2-(5-Acetyl-3-methylthien-2-yl)acetyl]-4-hydroxy-6-methyl-2H-pyran-2-one



C15 H14 O5 S; Mol wt: 306.3366

ACTION – Agent with the ability to promote cell proliferation, as demonstrated *in vitro* by potentiation of the erythropoietin-dependent proliferation of human erythroleukemia TF-1 cells. Potentially useful for promoting platelet, white blood cell and red blood cell production, as well as for cancer chemotherapy and radiotherapy, bone marrow transplantation therapy, and for the prevention and treatment of cytopenia arising from immune disorders or anemia.

SOURCE – Toray.

REFERENCES

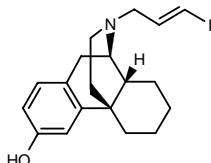
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TREATMENT OF POISONING, DRUG ABUSE AND DEPENDENCY

MCL-118

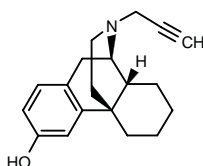
309711

17-(3-Iodo-2-propenyl)morphinan-3-ol



C₁₉ H₂₄ I N O; Mol wt: 409.3046

ACTION – Mixed mu and kappa opioid receptor agonist ($K_i = 0.0048$ and 0.037 nM, respectively) with 730-fold selectivity over delta opioid receptors. Potentially useful for the treatment of cocaine abuse. Another related compound is:



MCL-117 [309709]: C₁₉ H₂₃ N O

SOURCES – Harvard Medical School, Boston, MA (US); University of Rochester Medical Center, Rochester, NY (US).

REFERENCES

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DIAGNOSTIC AGENTS

PERFLUTREN LIPID MICROSPHERES

251977

Octafluoropropane-filled lipid microspheres (mean diameter 1.1-3.3 μ m) composed of octafluoropropane encapsulated in an outer lipid shell consisting of DPPA, DPPC and MPE5000 DPPE

DMP-115
MRX-115⁺
YM-454
Aerosomes™

ACTION – Lipid fluorocarbon echocardiographic contrast agent.

INDICATION – Contrast enhancement during echocardiographic procedures.

PRESENTATION – Single-use vial (2 ml) containing a clear liquid with 6.52 mg/ml octafluoropropane (perflutren) in the headspace, 0.75 mg/ml lipid blend (0.045 mg DPPA, 0.401 mg DPPC and 0.304 mg MPE5000 DPPE), 103.5 mg/ml propylene glycol, 126.2 mg/ml glycerin and 6.8 mg/ml sodium chloride in water for injection; upon activation with the aid of a Vialmix™, each ml of injectable suspension contains 1.2×10^{10} perflutren lipid microspheres and 150 μ l (1.1 mg) octafluoropropane.

PROPRIETARY NAME – Definity (CA, US).

SOURCE – Bristol-Myers Squibb.

REFERENCES

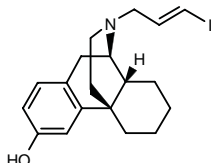
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TREATMENT OF POISONING, DRUG ABUSE AND DEPENDENCY

MCL-118

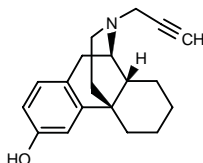
309711

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MCL-117 [309709]: C₁₉ H₂₃ N O

SOURCES – Harvard Medical School, Boston, MA (US); University of Rochester Medical Center, Rochester, NY (US).

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DIAGNOSTIC AGENTS

PERFLUTREN LIPID MICROSPHERES

251977

Octafluoropropane-filled lipid microspheres (mean diameter 1.1-3.3 μ m) composed of octafluoropropane encapsulated in an outer lipid shell consisting of DPPA, DPPC and MPE5000 DPPE

DMP-115
MRX-115⁺
YM-454
Aerosomes™

ACTION – Lipid fluorocarbon echocardiographic contrast agent.

INDICATION – Contrast enhancement during echocardiographic procedures.

PRESENTATION – Single-use vial (2 ml) containing a clear liquid with 6.52 mg/ml octafluoropropane (perflutren) in the headspace, 0.75 mg/ml lipid blend (0.045 mg DPPA, 0.401 mg DPPC and 0.304 mg MPE5000 DPPE), 103.5 mg/ml propylene glycol, 126.2 mg/ml glycerin and 6.8 mg/ml sodium chloride in water for injection; upon activation with the aid of a Vialmix™, each ml of injectable suspension contains 1.2×10^{10} perflutren lipid microspheres and 150 μ l (1.1 mg) octafluoropropane.

PROPRIETARY NAME – Definity (CA, US).

SOURCE – Bristol-Myers Squibb.

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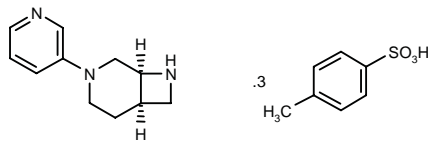
*Drug Data Rep 1997, 019(08): 0760.

ANALGESIC AND ANESTHETIC
DRUGS

ANALGESIC DRUGS

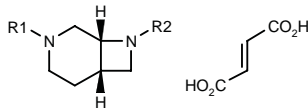
312483

cis-3-(3-Pyridyl)-3,8-diazabicyclo[4.2.0]octane tris(4-methylbenzenesulfonate)

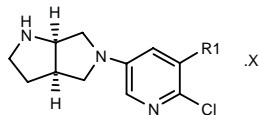


C11 H15 N3 . 3 C7 H8 O3 S; Mol wt: 705.8701

ACTION – Agent with the ability to control neurotransmitter release through modulation of acetylcholine receptors, proven to inhibit [³H]-cytisine binding to neuronal nicotinic acetylcholine receptors with a K_i of 0.02 nM. *In vivo*, compound gave minimum effective dose (MED) values of 1.9 and 0.62 μmol/kg i.p. in the mouse hot-plate paradigm and the rat formalin test, respectively. Potentially useful for the treatment of pain, as well as Alzheimer's disease, Parkinson's disease, attention deficit hyperactivity disorder, depression, nicotinic withdrawal syndrome, Tourette's syndrome and schizophrenia. Other exemplified diazabicyclic compounds include the following:



Compound	R1	R2	Isomer	Formula
312484	H	6-Cl-3-Pyr	1R,6S	C ₁₁ H ₁₄ ClN ₃ ·C ₄ H ₄ O ₄
312485	5-CN-3-Pyr	H	cis	C ₁₂ H ₁₄ N ₄ ·C ₄ H ₄ O ₄



Compound	R1	X	Formula
312486	H	2HCl	C ₁₁ H ₁₄ ClN ₃ ·2HCl
312487	Me	HCl	C ₁₂ H ₁₆ ClN ₃ ·HCl

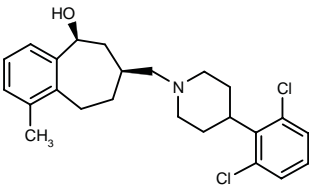
SOURCE – Abbott.

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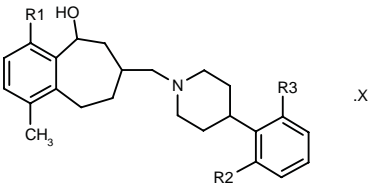
312603

(–)-*cis*-7-[4-(2,6-Dichlorophenyl)piperidin-1-ylmethyl]-1-methyl-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ol



C24 H29 Cl2 N O; Mol wt: 418.4051

ACTION – Agent with affinity for the opioid receptor-like ORL1 (N/OFQ) receptor, potentially useful for the treatment of chronic and acute pain. Other specifically claimed benzosuberonylpiperidine compounds are:



Compound	R1	R2	R3	Isomer	X	Formula
312604	H	Cl	Cl	racemic, cis	HCl	C ₂₄ H ₂₉ Cl ₂ NO·HCl
312605	Me	Cl	Cl	racemic		C ₂₅ H ₃₁ Cl ₂ NO
312606	Me	Me	Me	racemic	HCl	C ₂₇ H ₃₇ NO·HCl
312607	H	F	Cl	racemic, cis	HCl	C ₂₄ H ₂₉ ClFNO·HCl

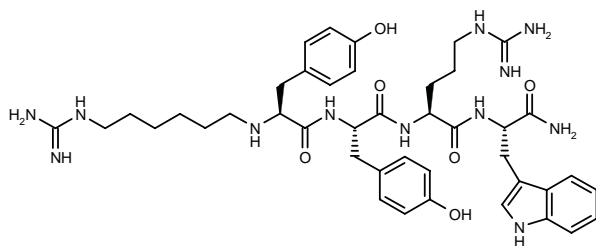
SOURCE – GlaxoSmithKline.

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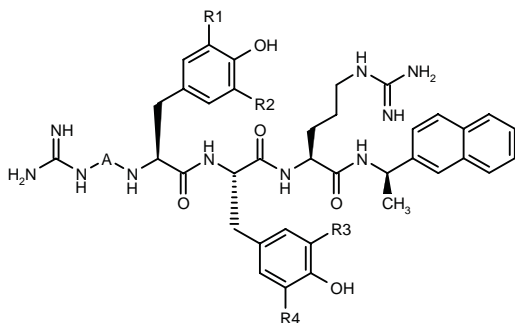
312788

N-(6-Guanidinohexyl)-L-tyrosyl-L-tyrosyl-L-arginyl-L-tryptophanamide



C42 H58 N12 O6; Mol wt: 826.9982

ACTION – Nociceptin (N/OFQ) receptor agonist (IC_{50} = 0.43 nM) with selectivity over mu opioid receptors (IC_{50} = 40 nM). It was active in the formalin test in rats and is potentially useful as an analgesic and anxiolytic agent. Other exemplified peptide derivatives include the following:



Compound	R1=R2	R3=R4	A	Formula
312789	H	H	-(CH2)5-	C ₄₂ H ₅₆ N ₁₀ O ₅
312790	Me	H	-(CH2)6-	C ₄₅ H ₆₂ N ₁₀ O ₅
312791	Me	Me	-(CH2)6-	C ₄₇ H ₆₆ N ₁₀ O ₅

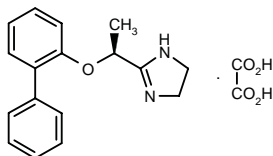
SOURCE – Nippon Shinyaku.

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313262

(-)-2-[1(*S*)-(Biphenyl-2-yloxy)ethyl]-4,5-dihydro-1*H*-imidazole oxalate



C17 H18 N2 O . C2 H2 O4; Mol wt: 356.3760

ACTION – α_2 -Adrenoceptor agonist with selectivity over imidazoline I₂ receptors (pK_i = 7.5 and 5.14, respectively), and functional selectivity over α_1 -adrenoceptors (pD_2 = 8.55 and 7.51, respectively, in isolated rat vas deferens). In mice, compound exhibited strong and long-lasting analgesic activity in both hot-plate and tail-flick paradigms (ED_{50} = 0.063 and 0.12 mg/kg s.c., respectively); analgesic activity was abolished by pretreatment with a selective α_2 -adrenoceptor antagonist.

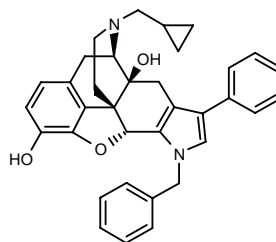
SOURCES – Università degli Studi di Bari, Bari (IT); Università degli Studi di Camerino, Camerino (IT); Université Louis Pasteur, Strasbourg (FR); Università degli Studi di Modena, Modena (IT).

REFERENCES

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313608

1'-Benzyl-17-(cyclopropylmethyl)-6,7-didehydro-4,5 α -epoxy-3,14 β -dihydroxy-4'-phenylpyrrolo[2',3':6,7]-morphinan



C35 H34 N2 O3; Mol wt: 530.6646

ACTION – Potent delta opioid receptor antagonist with high binding affinity for both delta and mu opioid receptors (K_i = 13.7 and 16.8 nM, respectively) and 8-fold selectivity over kappa opioid receptors. *In vivo*, in the mouse *p*-phenylquinone-induced abdominal stretch assay, compound antagonized the effect of the selective delta agonist SNC-80 (AD_{50} = 4.34 mg/kg s.c.) and it also inhibited the convulsive response to high doses of SNC-80. Potentially useful as an analgesic agent.

SOURCES – University of Bath, Bath (GB); University of Bristol, Bristol (GB); University of Michigan, Ann Arbor, MI (US); University of Virginia, Charlottesville, VA (US).

REFERENCES

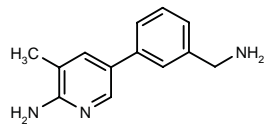
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ANTIMIGRAINE DRUGS

GW-289013

313081

5-[3-(Aminomethyl)phenyl]-3-methylpyridin-2-amine



C13 H15 N3; Mol wt: 213.2825

ACTION – Nitric oxide synthase inhibitor with selectivity for the human recombinant neuronal isoform (nNOS; IC₅₀ = 1.1 μM) over human recombinant endothelial (eNOS) and inducible (iNOS) isoforms (IC₅₀ = 156 and 33.5 μM, respectively). In rats, although compound (2 mg/kg/min i.v.) *per se* had no significant effect on blood pressure or vessel diameter, it caused a significant inhibition of neurogenic vasodilatation (31-40% compared to control animals), but not middle meningeal artery dilatation induced by acetylcholine. Potentially useful for the treatment of migraine.

SOURCE – GlaxoSmithKline.

REFERENCES

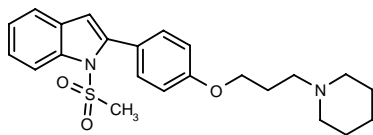
1. Honey, A.C. et al. *The nNOS inhibitor, GW289013, inhibits neurogenic vasodilation in the anaesthetised rat.* Br J Pharmacol 2001, 134(Suppl.): Abst 102P.

PSYCHOPHARMACOLOGIC DRUGS

TREATMENT OF SLEEP DISORDERS

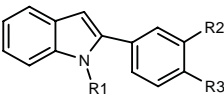
311801

1-(Methylsulfonyl)-2-[4-[3-(1-piperidinyl)propoxy]phenyl]-1*H*-indole



C23 H28 N2 O3 S; Mol wt: 412.5512

ACTION – Histamine H₃ receptor ligand (K_i = 7 nM), potentially useful for the treatment of sleep disorders, arousal/vigilance disorders, Alzheimer's disease, epilepsy, eating disorders, attention deficit hyperactivity disorder, learning and memory disorders, mild cognitive impairment, schizophrenia, migraine, allergic rhinitis and asthma. Other exemplified compounds from this series of phenyl-substituted indoles and indazoles include the following:



Compound	R1	R2	R3	Formula
311802	H	H	1-Pip-(CH2)3O	C ₂₂ H ₂₆ N ₂ O
311804	SO ₂ Me	H	1-Me-2-pyrrolidinyl-CH ₂ CH ₂ O	C ₂₂ H ₂₆ N ₂ O ₃ S
311807	SO ₂ Me	1-Pip-(CH ₂)3O	H	C ₂₃ H ₂₈ N ₂ O ₃ S

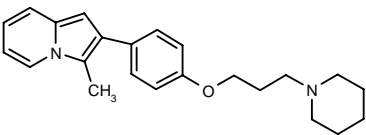
SOURCE – Ortho-McNeil.

REFERENCES

1. Breitenbucher, J.G. and Chai, W. (Ortho-McNeil Pharmaceutical, Inc.) *Phenyl-substd. indoles and indazoles.* WO 0174773.

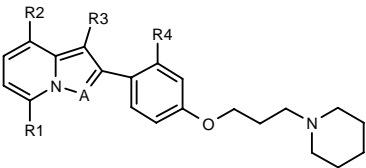
311810

3-Methyl-2-[4-[3-(1-piperidinyl)propoxy]phenyl]indolizine



C23 H28 N2 O; Mol wt: 348.4872

ACTION – Histamine H₃ receptor ligand (K_i = 1 nM), potentially useful for the treatment of sleep disorders, arousal/vigilance disorders, Alzheimer's disease, epilepsy, eating disorders, attention deficit hyperactivity disorder, learning and memory disorders, mild cognitive impairment, schizophrenia, migraine, allergic rhinitis and asthma. Other exemplified phenyl-substituted indolizines include the following:



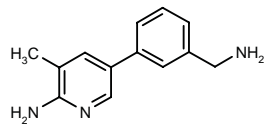
Compound	R1	R2	R3	R4	A	Formula
311811	H	H	H	H	CH	C ₂₂ H ₂₆ N ₂ O
311814	H	Me	H	H	CH	C ₂₃ H ₂₈ N ₂ O
311815	H	H	Me	H	CH	C ₂₃ H ₂₈ N ₂ O
311816	Me	H	H	H	CH	C ₂₃ H ₂₈ N ₂ O
311818	H	H	Me	Me	CH	C ₂₄ H ₃₀ N ₂ O
311819	H	H	Ph	H	CH	C ₂₈ H ₃₀ N ₂ O
311820	H	H	CH ₂ CH ₂ Ph	H	CH	C ₃₀ H ₃₄ N ₂ O
311821	H	H	Et	H	CH	C ₂₄ H ₃₀ N ₂ O
311822	H	H	H	H	C(Et)	C ₂₄ H ₃₀ N ₂ O
311823	H	H	H	H	N	C ₂₁ H ₂₅ N ₃ O

ANTIMIGRAINE DRUGS

GW-289013

313081

5-[3-(Aminomethyl)phenyl]-3-methylpyridin-2-amine



C13 H15 N3; Mol wt: 213.2825

ACTION – Nitric oxide synthase inhibitor with selectivity for the human recombinant neuronal isoform (nNOS; IC₅₀ = 1.1 μM) over human recombinant endothelial (eNOS) and inducible (iNOS) isoforms (IC₅₀ = 156 and 33.5 μM, respectively). In rats, although compound (2 mg/kg/min i.v.) *per se* had no significant effect on blood pressure or vessel diameter, it caused a significant inhibition of neurogenic vasodilatation (31-40% compared to control animals), but not middle meningeal artery dilatation induced by acetylcholine. Potentially useful for the treatment of migraine.

SOURCE – GlaxoSmithKline.

REFERENCES

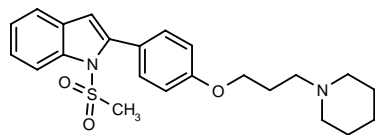
1. Honey, A.C. et al. *The nNOS inhibitor, GW289013, inhibits neurogenic vasodilation in the anaesthetised rat.* Br J Pharmacol 2001, 134(Suppl.): Abst 102P.

PSYCHOPHARMACOLOGIC DRUGS

TREATMENT OF SLEEP DISORDERS

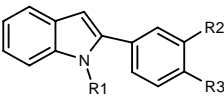
311801

1-(Methylsulfonyl)-2-[4-[3-(1-piperidinyl)propoxy]phenyl]-1*H*-indole



C23 H28 N2 O3 S; Mol wt: 412.5512

ACTION – Histamine H₃ receptor ligand (K_i = 7 nM), potentially useful for the treatment of sleep disorders, arousal/vigilance disorders, Alzheimer's disease, epilepsy, eating disorders, attention deficit hyperactivity disorder, learning and memory disorders, mild cognitive impairment, schizophrenia, migraine, allergic rhinitis and asthma. Other exemplified compounds from this series of phenyl-substituted indoles and indazoles include the following:



Compound	R1	R2	R3	Formula
311802	H	H	1-Pip-(CH2)3O	C ₂₂ H ₂₆ N ₂ O
311804	SO2Me	H	1-Me-2-pyrrolidinyl-CH2CH2O	C ₂₂ H ₂₆ N ₂ O ₃ S
311807	SO2Me	1-Pip-(CH2)3O	H	C ₂₃ H ₂₈ N ₂ O ₃ S

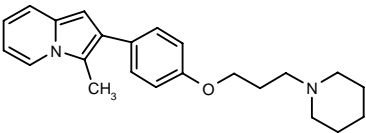
SOURCE – Ortho-McNeil.

REFERENCES

1. Breitenbucher, J.G. and Chai, W. (Ortho-McNeil Pharmaceutical, Inc.) *Phenyl-substd. indoles and indazoles.* WO 0174773.

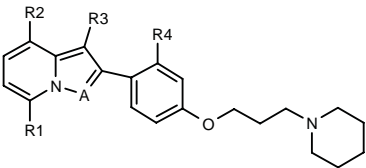
311810

3-Methyl-2-[4-[3-(1-piperidinyl)propoxy]phenyl]indolizine

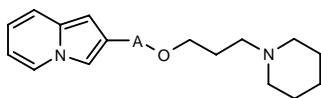


C23 H28 N2 O; Mol wt: 348.4872

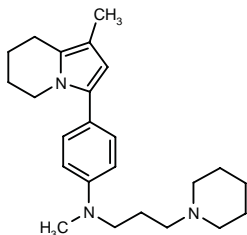
ACTION – Histamine H₃ receptor ligand (K_i = 1 nM), potentially useful for the treatment of sleep disorders, arousal/vigilance disorders, Alzheimer's disease, epilepsy, eating disorders, attention deficit hyperactivity disorder, learning and memory disorders, mild cognitive impairment, schizophrenia, migraine, allergic rhinitis and asthma. Other exemplified phenyl-substituted indolizines include the following:



Compound	R1	R2	R3	R4	A	Formula
311811	H	H	H	H	CH	C ₂₂ H ₂₆ N ₂ O
311814	H	Me	H	H	CH	C ₂₃ H ₂₈ N ₂ O
311815	H	H	Me	H	CH	C ₂₃ H ₂₈ N ₂ O
311816	Me	H	H	H	CH	C ₂₃ H ₂₈ N ₂ O
311818	H	H	Me	Me	CH	C ₂₄ H ₃₀ N ₂ O
311819	H	H	Ph	H	CH	C ₂₈ H ₃₀ N ₂ O
311820	H	H	CH2CH2Ph	H	CH	C ₃₀ H ₃₄ N ₂ O
311821	H	H	Et	H	CH	C ₂₄ H ₃₀ N ₂ O
311822	H	H	H	H	C(Et)	C ₂₄ H ₃₀ N ₂ O
311823	H	H	H	H	N	C ₂₁ H ₂₅ N ₃ O



Compound	A	Formula
311812	1,2-Ph	C ₂₂ H ₂₆ N ₂ O
311813	1,3-Ph	C ₂₂ H ₂₆ N ₂ O



311817: C24 H35 N3

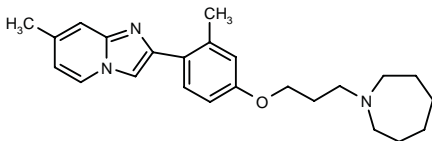
SOURCE – Ortho-McNeil.

REFERENCES

1. Chai, W. et al. (Ortho-McNeil Pharmaceutical, Inc.) *Phenyl-substd. indolizine derivs. and their use as histamine H3 ligands.* WO 0174814.

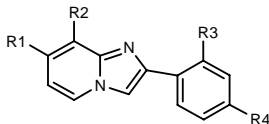
311825

7-Methyl-2-[2-methyl-4-[3-(perhydroazepin-1-yl)propoxy]phenyl]imidazo[1,2-a]pyridine

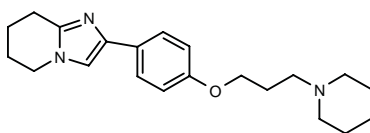


C24 H31 N3 O; Mol wt: 377.5289

ACTION – Histamine H₃ receptor ligand (K_i = 0.5 nM), potentially useful for the treatment of sleep disorders, arousal/vigilance disorders, Alzheimer’s disease, epilepsy, eating disorders, attention deficit hyperactivity disorder, learning and memory disorders, mild cognitive impairment, schizophrenia, migraine, allergic rhinitis and asthma. Other exemplified phenyl-substituted imidazo[1,2-a]pyridines include the following:



Compound	R1	R2	R3	R4	Formula
311826	H	Me	H	NHCH2CH2N(Et)2	C ₂₀ H ₂₆ N ₄
311827	Me	H	H	1-Pip-(CH2)3O	C ₂₂ H ₂₇ N ₃ O
311829	Me	H	H	1-pyrrolidinyl-(CH2)3O	C ₂₁ H ₂₅ N ₃ O
311830	Me	H	H	perhydro-1-azepinyl-(CH2)3O	C ₂₃ H ₂₉ N ₃ O
311831	Me	H	Me	1-Pip-(CH2)3O	C ₂₃ H ₂₉ N ₃ O
311832	H	Me	H	1-Pip-(CH2)3O	C ₂₂ H ₂₇ N ₃ O



311828: C21 H29 N3 O

SOURCE – Ortho-McNeil.

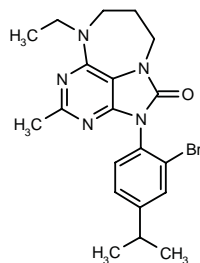
REFERENCES

1. Breitenbucher, J.G. et al. (Ortho-McNeil Pharmaceutical, Inc.) *Phenyl-substd. imidazopyridines.* WO 0174815.

ANXIOLYTICS

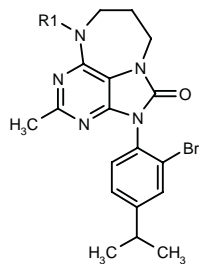
312667

4-(2-Bromo-4-isopropylphenyl)-10-ethyl-2-methyl-4,5,7,8,9,10-hexahydro[1,4]diazepino[1,2,3-*gh*]purin-5-one



C20 H24 Br N5 O; Mol wt: 430.3476

ACTION – Corticotropin-releasing factor (CRF) antagonist, potentially useful for the treatment of anxiety, depression and other disorders related to CRF over-expression. Other compounds within this series of tricyclic fused pyrimidine and pyridine derivatives include the following:



Compound	R1	Formula
312668	cyclopropyl-CH2	C ₂₂ H ₂₆ BrN ₅ O
312669	Bu	C ₂₂ H ₂₈ BrN ₅ O
312670	C5H11	C ₂₃ H ₃₀ BrN ₅ O
312671	CH(Et)2	C ₂₃ H ₃₀ BrN ₅ O
312672	CH2Ph	C ₂₅ H ₂₈ BrN ₅ O

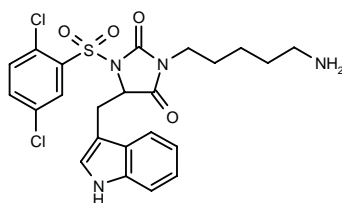
SOURCE – Bristol-Myers Squibb.

REFERENCES

1. Bakthavatachalam, R. (DuPont Pharmaceuticals Co.) *Tricyclic fused pyridine and pyrimidine derivs. as CRF receptor antagonists.* WO 0183486.

313018

3-(5-Aminopentyl)-1-(2,5-dichlorophenylsulfonyl)-5-(1*H*-indol-3-ylmethyl)imidazolidine-2,4-dione



C₂₃ H₂₄ Cl₂ N₄ O₄ S; Mol wt: 523.4386

ACTION – A representative compound from a series of hydantoin derivatives effective as somatostatin sst₂ receptor agonists. Compound is considered to have potential in the treatment of anxiety, depression, schizophrenia, neurodegenerative diseases such as dementia, epilepsy, endocrinological disorders associated with excess hormonal release, cancer, vascular disorders and immunological diseases.

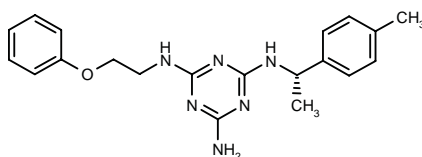
SOURCE – Novartis.

REFERENCES

1. Berney, D. et al. (Novartis AG;Novartis-Erfindungen VmbH) *Hydantoin derivs. with affinity for somatostatin receptors*. WO 0185718.

313206

*N*²-[1(*S*)-(4-Methylphenyl)ethyl]-*N*⁴-(2-phenoxyethyl)-1,3,5-triazine-2,4,6-triamine



C₂₀ H₂₄ N₆ O; Mol wt: 364.4506

ACTION – A representative compound from a series of pyrimidines and triazines with 5-HT₇ receptor-antagonist activity. This compound gave an ID₅₀ of 23.8 mg/kg in the rat pup isolation-induced ultrasonic vocalization test, suggesting anxiolytic and antidepressant activity. Potentially useful for the treatment of sleep disorders, depression, schizophrenia, anxiety, obsessive-compulsive disorders, circadian rhythm disorders, ocular disorders and centrally and peripherally mediated hypertension.

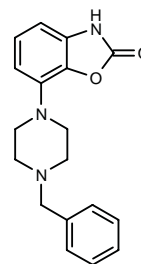
SOURCE – Bristol-Myers Squibb.

REFERENCES

1. Poss, M.A. et al. (Bristol-Myers Squibb Co.) *5-HT₇ receptor antagonists*. WO 0185701.

313207

7-(4-Benzylpiperazin-1-yl)benzoxazol-2(3*H*)-one



C₁₈ H₁₉ N₃ O₂; Mol wt: 309.3671

ACTION – A representative compound from a series of piperazine and piperidine derivatives combining dopamine D₂ agonist-activity and affinity for 5-HT and/or norenergic receptors. Potentially useful in the treatment of anxiety, depression, Parkinson's disease and drug abuse.

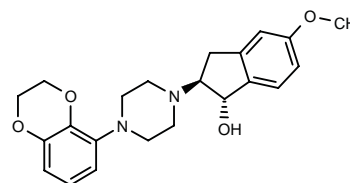
SOURCE – Solvay.

REFERENCES

1. Feenstra, R.W. et al. (Solvay Pharmaceuticals BV) *Piperazine and piperidine cpds*. EP 1153925, WO 0185725.

313275

(±)-*trans*-2-[4-(2,3-Dihydro-1,4-benzodioxin-5-yl)piperazin-1-yl]-5-methoxyindan-1-ol



C₂₂ H₂₆ N₂ O₄; Mol wt: 382.4574

ACTION – High affinity 5-HT_{1A} receptor ligand (pK_i = 8.9) with 224-fold selectivity over α₁-adrenoceptors (pK_i = 6.55), partial agonist activity at human 5-HT_{1A} receptors and *in vivo* inhibitory activity against the hypothermia induced by 8-OH-DPAT. Compound exhibited good stability in human microsomes. Its (–)-isomer [314630] exhibited good oral bioavailability in rats (47%) and was active in rat models predictive of anxiolytic activity such as the ultrasonic vocalization and social interaction tests. Potentially useful as an anxiolytic agent.

SOURCE – Servier.

REFERENCES

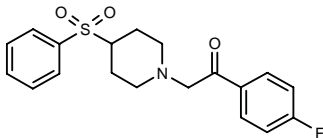
1. Peglion, J.-L. et al. (ADIR et Cie.) *Indanol derivs., process for their preparation and pharmaceutical compsns. containing them*. CA 2249756, EP 0906912, FR 2769312, JP 1999158179, US 5958927, US 6060487.

2. Peglion, J.-L. et al. *Improvement in the selectivity and metabolic stability of the serotonin 5-HT_{1A} ligand, S 15535: A series of cis- and trans-2-(arylcycloalkylamine) 1-indanols*. J Med Chem 2002, 45(1): 165.

ANTIPSYCHOTIC DRUGS

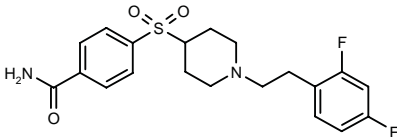
313623

1-(4-Fluorophenyl)-2-[4-(phenylsulfonyl)piperidin-1-yl]ethanone



C19 H20 F N O3 S; Mol wt: 361.4350

ACTION – 5-HT_{2A} receptor antagonist with nanomolar affinity for rat and human receptors (K_i = 0.51 and 2.4 nM, respectively) and high selectivity over human 5-HT_{2C} and dopamine D2 receptors (K_i = 130 and > 1500 nM, respectively), as well as α_1 -adrenoceptors and the outward delayed rectifier potassium channel IK_r (K_i > 1500 nM). Compound exhibited a good pharmacokinetic profile, with 30% oral bioavailability, and did not induce cardiac dysrhythmia in ferrets at up to 10 mg/kg i.v. Potentially useful as an antipsychotic agent. Another related compound is:



313622: C20 H22 F2 N2 O3 S

SOURCE – Merck Sharp & Dohme.

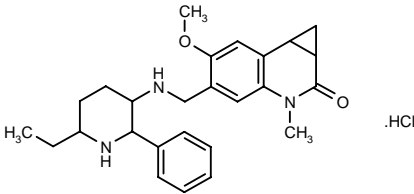
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1. Blurton, P. et al. (Merck Sharp & Dohme Ltd.) *Phenylsulphonyl derivs. as 5-HT receptor ligands*. EP 1147083, WO 0043362.
2. Fletcher, S.R. et al. *4-(Phenylsulfonyl)piperidines: Novel, selective, and bioavailable 5-HT_{2A} receptor antagonists*. J Med Chem 2002, 45(2): 492.

TREATMENT OF MOOD DISORDERS

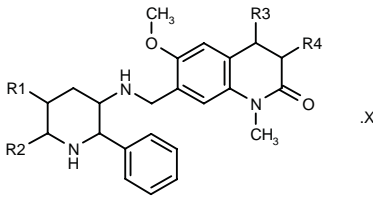
312046

5-(6-Ethyl-2-phenylpiperidin-3-ylaminomethyl)-6-methoxy-3-methyl-1a,2,3,7b-tetrahydro-1H-cyclopropa[c]quinolin-2-one hydrochloride



C26 H33 N3 O2 . HCl; Mol wt: 456.0266

ACTION – Tachykinin NK₁ receptor antagonist with potential in the treatment of a broad range of conditions including CNS disorders such as depression, anxiety, schizophrenia, Parkinson's disease, Alzheimer's disease, Huntington's disease and drug abuse, acute and chronic pain, migraine, multiple sclerosis, amyotrophic lateral sclerosis, cerebral infarction, respiratory inflammatory diseases including chronic obstructive airways disease, bronchopneumonia, chronic bronchitis, cystic fibrosis and adult respiratory distress syndrome, inflammatory disorders such as arthritis, asthma and allergies, HIV infection, ophthalmic diseases, cancer, gastrointestinal inflammatory disorders, urinary incontinence, cardiovascular disorders, sexual dysfunction and eating disorders. Other specifically claimed piperidine-containing compounds include the following:



Compound	R1	R2	R3	R4	Isomer	X	Formula
312047	H	Me	-CH2-		1aS,5(2R,3R,6R),7bR	HCl	C ₂₅ H ₃₁ N ₃ O ₂ ·HCl
312048	H	Et	H	H		HCl	C ₂₅ H ₃₃ N ₃ O ₂ ·HCl
312049	H	Et	-CH2-		1aR,5(2R,3R,6R),7bS	D-lactate	C ₂₆ H ₃₃ N ₃ O ₂ ·C ₃ H ₆ O ₃
312050	H	Me	H	H		D-lactate	C ₂₄ H ₃₁ N ₃ O ₂ ·C ₃ H ₆ O ₃
312051	H	Et	-CH2-		1aR,5(2S,3S,6S),7bS	L-lactate	C ₂₆ H ₃₃ N ₃ O ₂ ·C ₃ H ₆ O ₃
312053	H	Me	-CH2-		1aS,5(2R,3R,6R),7bR	L-lactate	C ₂₅ H ₃₁ N ₃ O ₂ ·C ₃ H ₆ O ₃
312054	Et	H	-CH2-			D-lactate	C ₂₆ H ₃₃ N ₃ O ₂ ·C ₃ H ₆ O ₃
312055	Pr	H	-CH2-			D-lactate	C ₂₇ H ₃₅ N ₃ O ₂ ·C ₃ H ₆ O ₃

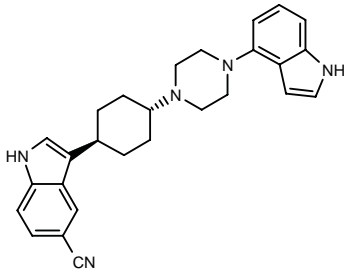
SOURCE – Pfizer.

REFERENCES

1. Arnold, E.P. et al. (Pfizer Products Inc.) *Benzoamide piperidine containing cpds. and related cpds*. WO 0177100.

313010

trans-3-[4-[4-(1H-Indol-4-yl)piperazin-1-yl]cyclohexyl]-1H-indole-5-carbonitrile



C27 H29 N5; Mol wt: 423.5611

ACTION – A representative compound from a series of cyclohexyl-substituted piperazines that act as dual 5-HT_{1A} autoreceptor antagonists and 5-HT uptake inhibitors. In *in vitro* testing, it displayed K_i values of 3.51 and 4.19 nM, respectively, against the 5-HT_{1A} receptor and the 5-HT transporter. Potentially useful for the treatment of depression.

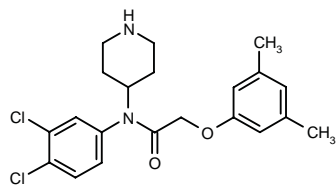
SOURCE – Wyeth Pharmaceuticals.

REFERENCES

1. Mewshaw, R.E. et al. (American Home Products Corp.) *Arylpiperaziny-cyclohexyl indole derivs. for the treatment of depression*. US 6313126.

314257

N-(3,4-Dichlorophenyl)-2-(3,5-dimethylphenoxy)-*N*-(4-piperidinyl)acetamide



C21 H24 Cl2 N2 O2; Mol wt: 407.3386

ACTION – Dual neurokinin NK₁ antagonist and 5-HT reuptake inhibitor with high binding affinity for NK₁ receptors and the 5-HT transporter (pIC₅₀ = 7.6 and 7.5, respectively). Compound antagonized substance P-induced contractions in isolated guinea pg ileum (pA₂ = 6.88) and blocked 5-HT reuptake in rats, as demonstrated in microdialysis experiments in freely moving animals, where it increased extracellular 5-HT levels up to 350% of baseline at a dose of 35 μmol/kg i.p. Potentially useful as an antidepressant.

SOURCE – UCB Pharma.

REFERENCES

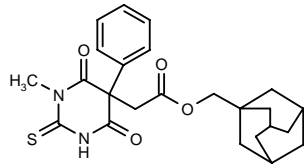
1. Ryckmans, T. et al. *First dual NK1 antagonists-serotonin reuptake inhibitors: Synthesis and SAR of a new class of potential antidepressants*. Bioorg Med Chem Lett 2002, 12(2): 261.

NEUROLOGIC DRUGS

ANTIEPILEPTIC DRUGS

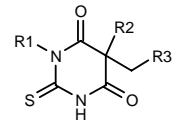
312507

2-(1-Methyl-4,6-dioxo-5-phenyl-2-thioxoperhydro-pyrimidin-5-yl)acetic acid adamantan-1-ylmethyl ester



C24 H28 N2 O4 S; Mol wt: 440.5612

ACTION – Ultra-short-acting hypnotic barbiturate that is rapidly metabolized and highly effective. It induced sleep in rats within 10 min after administration of 50 mg/kg i.p. and the duration of the hypnotic effect was < 1 h. Also useful for the treatment of convulsions. Other exemplified compounds are:



Compound	R1	R2	R3	Formula
312508	Me	Ph	t-BuCH2OCO	C ₁₈ H ₂₂ N ₂ O ₄ S
312509	Me	Ph	i-BuOCO	C ₁₇ H ₂₀ N ₂ O ₄ S
312510	Me	Ph	cyclohexyl-OCO	C ₁₉ H ₂₂ N ₂ O ₄ S
312511	Me	2-cyclopentenyl	1-adamantyl-CH2OCO	C ₂₃ H ₃₀ N ₂ O ₄ S
312512	Me	2-cyclopentenyl	t-BuCH2OCO	C ₁₇ H ₂₄ N ₂ O ₄ S
312513	Me	2-cyclopentenyl	i-BuOCO	C ₁₆ H ₂₂ N ₂ O ₄ S
312514	Me	2-cyclopentenyl	cyclohexyl-OCO	C ₁₈ H ₂₄ N ₂ O ₄ S
312515	CH2CO2Et	allyl	i-Bu	C ₁₆ H ₂₄ N ₂ O ₄ S
312516	CO2Et	allyl	i-Bu	C ₁₅ H ₂₂ N ₂ O ₄ S

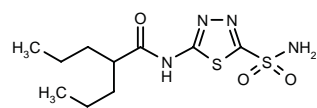
SOURCE – ARYx Therapeutics.

REFERENCES

1. Druzgala, P. and Milner, P.G. (ARYx Therapeutics, Inc.) *Ultrasort acting hypnotic barbiturates*. WO 0181319.

313640

2-Propyl-*N*-(5-sulfamoyl-1,3,4-thiadiazol-2-yl)pent-anamide



C10 H18 N4 O3 S2; Mol wt: 306.4092

ACTION – Anticonvulsant, a carbonic anhydrase inhibitor (K_i = 50, 6 and 25 nM, respectively, against human carbonic anhydrase type I and II and bovine lung microsomal carbonic anhydrase type IV) that incorporates valproic acid and the sulfonamide residue of acetazolamide. In the maximal electroshock (MES) seizure test in mice, a dose of 30 mg/kg i.p. provided 96 and 93% protection at 0.5 and 3 h, respectively, and a dose of 10 mg/kg i.p. provided 25 and 100% protection, respectively, at the same times. Significant anticonvulsant activity (63%) was still evident at 6 h after the higher dose. Potentially useful for the treatment of conditions associated with high intracranial pressure such as epilepsy, genetic hemiplegic migraine and ataxia, tardive dyskinesia and essential tremors in Parkinson’s disease.

SOURCES – Università degli Studi di Firenze, Firenze (IT); University of Namur, Namur (BE).

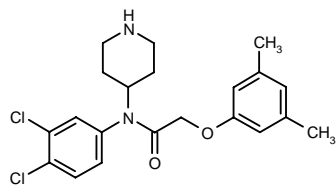
SOURCE – Wyeth Pharmaceuticals.

REFERENCES

1. Mewshaw, R.E. et al. (American Home Products Corp.) *Arylpiperaziny-cyclohexyl indole derivs. for the treatment of depression*. US 6313126.

314257

N-(3,4-Dichlorophenyl)-2-(3,5-dimethylphenoxy)-*N*-(4-piperidinyl)acetamide



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ACTION – Dual neurokinin NK₁ antagonist and 5-HT reuptake inhibitor with high binding affinity for NK₁ receptors and the 5-HT transporter (pIC₅₀ = 7.6 and 7.5, respectively). Compound antagonized substance P-induced contractions in isolated guinea pg ileum (pA₂ = 6.88) and blocked 5-HT reuptake in rats, as demonstrated in microdialysis experiments in freely moving animals, where it increased extracellular 5-HT levels up to 350% of baseline at a dose of 35 μmol/kg i.p. Potentially useful as an antidepressant.

SOURCE – UCB Pharma.

REFERENCES

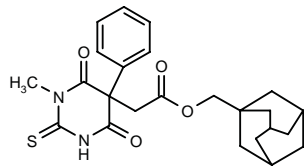
1. Ryckmans, T. et al. *First dual NK1 antagonists-serotonin reuptake inhibitors: Synthesis and SAR of a new class of potential antidepressants*. Bioorg Med Chem Lett 2002, 12(2): 261.

NEUROLOGIC DRUGS

ANTIEPILEPTIC DRUGS

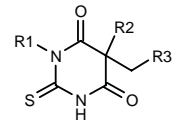
312507

2-(1-Methyl-4,6-dioxo-5-phenyl-2-thioxoperhydro-pyrimidin-5-yl)acetic acid adamantan-1-ylmethyl ester



C24 H28 N2 O4 S; Mol wt: 440.5612

ACTION – Ultra-short-acting hypnotic barbiturate that is rapidly metabolized and highly effective. It induced sleep in rats within 10 min after administration of 50 mg/kg i.p. and the duration of the hypnotic effect was < 1 h. Also useful for the treatment of convulsions. Other exemplified compounds are:



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312509	Me	Ph	i-BuOCO	C ₁₇ H ₂₀ N ₂ O ₄ S
312510	Me	Ph	cyclohexyl-OCO	C ₁₉ H ₂₂ N ₂ O ₄ S
312511	Me	2-cyclopentenyl	1-adamantyl-CH2OCO	C ₂₃ H ₃₀ N ₂ O ₄ S
312512	Me	2-cyclopentenyl	t-BuCH2OCO	C ₁₇ H ₂₄ N ₂ O ₄ S
312513	Me	2-cyclopentenyl	i-BuOCO	C ₁₆ H ₂₂ N ₂ O ₄ S
312514	Me	2-cyclopentenyl	cyclohexyl-OCO	C ₁₈ H ₂₄ N ₂ O ₄ S
312515	CH2CO2Et	allyl	i-Bu	C ₁₆ H ₂₄ N ₂ O ₄ S
312516	CO2Et	allyl	i-Bu	C ₁₅ H ₂₂ N ₂ O ₄ S

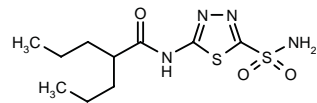
SOURCE – ARYx Therapeutics.

REFERENCES

1. Druzgala, P. and Milner, P.G. (ARYx Therapeutics, Inc.) *Ultrasort acting hypnotic barbiturates*. WO 0181319.

313640

2-Propyl-*N*-(5-sulfamoyl-1,3,4-thiadiazol-2-yl)pent-anamide



C10 H18 N4 O3 S2; Mol wt: 306.4092

ACTION – Anticonvulsant, a carbonic anhydrase inhibitor (K_i = 50, 6 and 25 nM, respectively, against human carbonic anhydrase type I and II and bovine lung microsomal carbonic anhydrase type IV) that incorporates valproic acid and the sulfonamide residue of acetazolamide. In the maximal electroshock (MES) seizure test in mice, a dose of 30 mg/kg i.p. provided 96 and 93% protection at 0.5 and 3 h, respectively, and a dose of 10 mg/kg i.p. provided 25 and 100% protection, respectively, at the same times. Significant anticonvulsant activity (63%) was still evident at 6 h after the higher dose. Potentially useful for the treatment of conditions associated with high intracranial pressure such as epilepsy, genetic hemiplegic migraine and ataxia, tardive dyskinesia and essential tremors in Parkinson’s disease.

SOURCES – Università degli Studi di Firenze, Firenze (IT); University of Namur, Namur (BE).

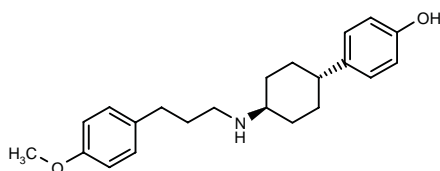
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2. Supuran, C.T. et al. *Carbonic anhydrase inhibitors. 10. New derivatives of 1,3,4-thiadiazole-2-sulfonamide and 4-methyl-2-sulfonamido-Δ²-1,3,4-thiadiazoline*. Rev Roum Chim 1992, 37(2): 289.

TREATMENT OF EXTRAPYRAMIDAL MOVEMENT DISORDERS

312351

trans-4-[4-[3-(4-Methoxyphenyl)propylamino]cyclohexyl]phenol



C22 H29 N O₂; Mol wt: 339.4761

ACTION – A representative compound from a series of cyclohexylamine derivatives with NMDA receptor-antagonist activity that gave an IC₅₀ of 0.07 μM against NR1A/NR2B NMDA receptor subtypes expressed in *Xenopus* oocytes. Potentially useful for the treatment of Parkinson's disease, as well as stroke, trauma, hypoglycemia, neurodegenerative disorders, anxiety, depression, migraine, convulsions, psychosis, glaucoma, cytomegalovirus-related retinitis, opioid tolerance and withdrawal, chronic pain and urinary incontinence.

SOURCE – Pfizer.

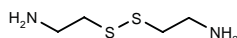
REFERENCES

1. Deorazio, R.J. et al. (Pfizer Inc.) *Cyclohexylamine deriv. as subtype selective NMDA receptor antagonists*. WO 0181295.

CYSTAMINE

314845

2-(2-Aminoethylsulfanyl)ethylamine



C4 H12 N₂ S₂; Mol wt: 152.2848

ACTION – Neuroprotective agent, a competitive transglutaminase (TGase) inhibitor that acts by blocking access to the active site of the enzyme for glutamine residues in proteins such as huntingtin. In the transgenic R6/2 mouse model of Huntington's disease, compound entered the brain following single or multiple i.p. doses and inhibited TGase activity. When given to the transgenic mice after the appearance of abnormal movements, it prolonged survival and reduced tremor, abnormal movements and weight loss. No effect on neuronal nuclear inclusions could be detected and compound increased transcription of the dnaj (*HDJ1* in humans)

gene, known to be neuroprotective for polyglutamine toxicity in *Drosophila*. Potentially useful for the treatment of Huntington's disease.

SOURCES – University of Kentucky, Lexington, KY (US); University of New Mexico, NM (US); Stanford University, Stanford, CA (US).

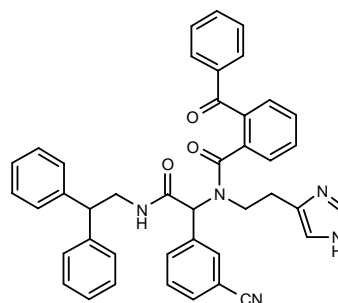
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TREATMENT OF IMMUNOLOGIC NEUROMUSCULAR DISORDERS

313250

2-Benzoyl-*N*-[1-(3-cyanophenyl)-1-[*N*-(2,2-diphenylethyl)carbamoyl]methyl]-*N*-[2-(1*H*-imidazol-4-yl)ethyl]benzamide



C42 H35 N₅ O₃; Mol wt: 657.7705

ACTION – TNF-α signaling modulator with an IC₅₀ of 0.41 μM against TNF-α-induced apoptosis in L929 cells and of 24.4 μM against TNF-α-induced VCAM expression in human umbilical vein endothelial cells. Compound demonstrated *in vivo* activity in animal models of multiple sclerosis (mice, i.p. administration), sepsis (mice, i.p. administration) and inflammatory bowel disease (rats, p.o. administration).

SOURCE – Genzyme General.

REFERENCES

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ANTI-CD154 MAb

314541

Anti-CD40L (CD154) monoclonal antibody

MR-1

ACTION – Anti-CD154 monoclonal antibody proven to block the CD40–CD154 costimulatory pathway and relapses in mice with experimental autoimmune encephalomyelitis (EAE). Short-term treatment of EAE mice at the time of immunization resulted in long-term inhibition of disease; whereas control mice all developed disease within the first 20 days, only 2 of 16 animals treated with the antibody developed mild and short-lasting clinical signs of disease. This long-term therapeutic effect was not accompanied by an effect on Th1 development or Th1/Th2 balance. Moreover the anti-CD154-treated mice showed reduced inflammatory responses. Potentially useful for the long-term treatment of multiple sclerosis not associated with persistent or latent CNS infection.

SOURCE – Northwestern University, Evanston, IL (US).

REFERENCES

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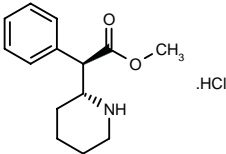
TREATMENT OF ATTENTION DEFICIT HYPERACTIVITY DISORDER

DEXMETHYLPHENIDATE HYDROCHLORIDE

273095

2(R)-Phenyl-2-[2(R)-piperidinyl]acetic acid methyl ester hydrochloride

d-threo-Methylphenidate hydrochloride
(+)-threo-Methylphenidate hydrochloride
d-MPH



C14 H19 N O2 . HCl; Mol wt: 269.7700

ACTION – Central nervous system stimulant.

INDICATION – Treatment of attention deficit hyperactivity disorder (ADHD) in children 7-12 years and adult patients.

PRESENTATION – Tablets, 2.5, 5 and 10 mg.

PROPRIETARY NAME – Focalin (US).

SOURCES – Celgene; marketed by Novartis.

REFERENCES

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5. Axten, J.M. et al. *Enantioselective synthesis of D-threo-methylphenidate.* J Am Chem Soc 1999, 121(27): 6511.

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9. Gilmore, A. and Milne, R. *Methylphenidate in children with hyperactivity: Review and cost-utility analysis.* Pharmacoeconom Drug Saf 2001, 10(2): 85.

10. Gonzalez, M. et al. *Pharmacokinetics of transdermal methylphenidate in pediatric patients with attention deficit hyperactivity disorder (ADHD).* Annu Meet Am Assoc Pharm Sci (AAPS) (Nov 14-18, New Orleans) 1999, Abst.

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13. Levin, E.D. et al. *Effects of chronic nicotine and methylphenidate in adults with attention deficit/hyperactivity disorder.* Exp Clin Psychopharmacol 2001, 9(1): 83.

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17. Thiruchelvam, D. et al. *Moderators and mediators of long-term adherence to stimulant treatment in children with ADHD.* J Am Acad Child Adolesc Psychiatry 2001, 40(8): 922.

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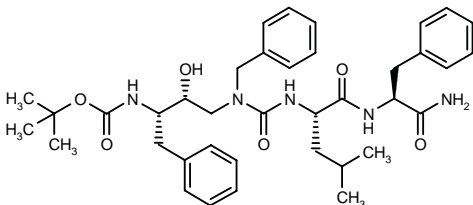
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32. Pivotal data presented for Celgene's ADD/ADHD therapy. DailyDrugNews.com (Daily Essentials) 1999, Oct 27.
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TREATMENT OF COGNITION DISORDERS

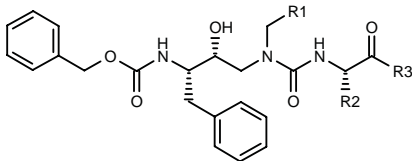
310169

N-[*N*-Benzyl-*N*-[3(*S*)-(*tert*-butoxycarbonylamino)-2(*R*)-hydroxy-4-phenylbutyl]carbamoyl]-*L*-leucyl-*L*-phenylalaninamide



C38 H51 N5 O6; Mol wt: 673.8499

ACTION – Peptidomimetic compound that acts as a γ -secretase inhibitor and thereby prevents the formation of β -amyloid peptide (A β). Potentially useful for the treatment and prevention of Alzheimer's disease. Other specially claimed compounds include the following:



Compound	R1	R2	R3	Formula
310170	4-Cl-Ph	i-Bu	-L-Phe-NH2	C ₄₁ H ₄₆ ClN ₅ O ₆
310171	2-Cl-Ph	i-Bu	-L-Phe-NH2	C ₄₁ H ₄₆ ClN ₅ O ₆
310172	2-furyl	i-Bu	-L-Phe-NH2	C ₃₉ H ₄₇ N ₅ O ₇
310173	CH2Ph	Ph	-L-Phe-NH2	C ₄₄ H ₄₇ N ₅ O ₆
310174	CH2Ph	i-Bu	-L-Nle-NH2	C ₃₉ H ₅₃ N ₅ O ₆
310175	CH2Ph	i-Bu	-L-Ile-NH2	C ₃₉ H ₅₃ N ₅ O ₆

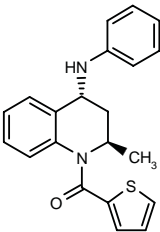
SOURCE – Merck Sharp & Dohme.

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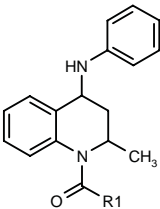
311796

trans-1-[2-Methyl-4-(phenylamino)-1,2,3,4-tetrahydroquinolin-1-yl]-1-(thien-2-yl)methanone



C21 H20 N2 O S; Mol wt: 348.4680

ACTION – Agent with the ability to increase the secretion of soluble β -amyloid precursor protein (sAPP), producing a 3-fold increase in sAPP secretion in PC-12 cells. At 1 μ M, compound also produced an 86.63% survival rate of glutamic acid-challenged PC-12 cells. Potentially useful in the treatment of Alzheimer's disease, Parkinson's disease, prion diseases, neuropathies, senile dementia and cerebrovascular-related neuronal disorders. Other exemplified compounds are:



Compound	R1	Isomer	Formula
311797	2-furyl	cis	C ₂₁ H ₂₀ N ₂ O ₂
311798	3,4-(MeO)2-Ph	cis	C ₂₅ H ₂₆ N ₂ O ₃
311799	2-furyl	trans	C ₂₁ H ₂₀ N ₂ O ₂

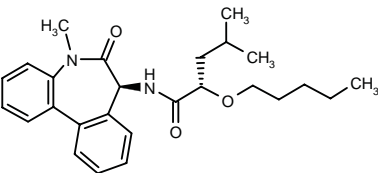
SOURCE – Takeda.

REFERENCES

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311978

4-Methyl-*N*-[5-methyl-6-oxo-6,7-dihydro-5 *H*-dibenzo[*b,d*]azepin-7(*S*)-yl]-2(*S*)-(pentyloxy)pentanamide



C26 H34 N2 O3; Mol wt: 422.5656

ACTION – A specifically claimed compound within a series of substituted lactams that inhibit β -amyloid peptide (A β) biosynthesis. It is reported to act through inhibition of γ -secretase, and is claimed for use in the treatment of Alzheimer's disease.

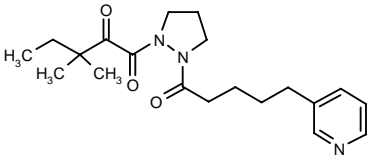
SOURCE – Bristol-Myers Squibb.

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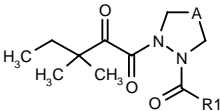
312268

3,3-Dimethyl-1-[2-[5-(3-pyridyl)pentanoyl]pyrazolidin-1-yl]pentane-1,2-dione

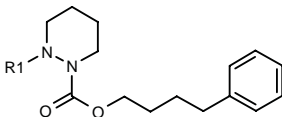


C20 H29 N3 O3; Mol wt: 359.4671

ACTION – Agent with the ability to stimulate neuronal regeneration while being devoid of immunosuppressive activity. This compound induced a 57% recovery of MPTP-challenged dopaminergic neurons in mice at 10 mg/kg p.o. Potentially useful for the treatment of neurodegenerative diseases including Alzheimer’s disease, Parkinson’s disease, Huntington’s disease and amyotrophic lateral sclerosis. Its use in the treatment of neurological disorders caused by stroke and brain and spinal cord trauma is also claimed. Other exemplified cyclic diaza-containing compounds are:



Compound	R1	A	Formula
312269	(CH2)4Ph	-CH2-	C ₂₁ H ₃₀ N ₂ O ₃
312270	CH2CH2Ph	-CH2-	C ₁₉ H ₂₆ N ₂ O ₃
312271	3-Pyr-ethynylene-CH2CH2	-CH2-	C ₂₀ H ₂₅ N ₃ O ₃
312272	(CH2)3Ph	-CH2-	C ₂₀ H ₂₈ N ₂ O ₃
312273	(CH2)5Ph	-CH2-	C ₂₂ H ₃₂ N ₂ O ₃
312274	(CH2)5Ph	-(CH2)2-	C ₂₃ H ₃₄ N ₂ O ₃
312275	3-Pyr-(CH2)5	-(CH2)2-	C ₂₂ H ₃₃ N ₃ O ₃
312276	O(CH2)3Ph	-(CH2)2-	C ₂₁ H ₃₀ N ₂ O ₄
312277	O(CH2)4Ph	-(CH2)2-	C ₂₂ H ₃₂ N ₂ O ₄
312279	O(CH2)5Ph	-(CH2)2-	C ₂₃ H ₃₄ N ₂ O ₄
312280	3-Pyr-(CH2)4O	-(CH2)2-	C ₂₁ H ₃₁ N ₃ O ₄
312281	(CH2)4Ph	-(CH2)2-	C ₂₂ H ₃₂ N ₂ O ₃



Compound	R1	Formula
312283	SO2CH2Ph	C ₂₂ H ₂₈ N ₂ O ₄ S
312285	cyclohexyl-NHCO	C ₂₂ H ₃₃ N ₃ O ₃

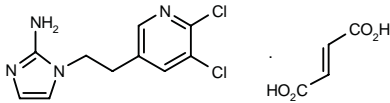
SOURCE – GPI Nil Holdings.

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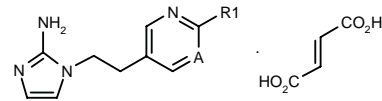
312480

1-[2-(5,6-Dichloropyridin-3-yl)ethyl]-1H-imidazol-2-amine fumarate



C10 H10 Cl2 N4 . C4 H4 O4; Mol wt: 373.1946

ACTION – An α4β2 nicotinic acetylcholine receptor agonist shown to inhibit [³H]-cytisine binding to α4β2 receptors with a K_i of 3.1 nM and to have > 10,000-fold selectivity over α1β1γδ receptors. This compound was able to activate α4β2 receptors expressed in *Xenopus* oocytes with an ED₅₀ of 2.4 μM. Potentially useful for the treatment of Alzheimer’s disease, Parkinson’s disease, cerebrovascular dementia, Tourette’s syndrome, neurosis during cerebral infarction, anxiety and schizophrenia. Other exemplified heterocyclic compounds include the following:



Compound	R1	A	Formula
312481	Cl	CH	C ₁₀ H ₁₁ ClN ₄ .C ₄ H ₄ O ₄
312482	H	N	C ₉ H ₁₁ N ₅ .C ₄ H ₄ O ₄

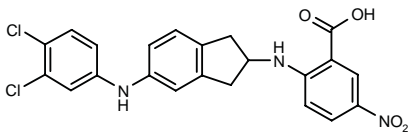
SOURCE – Suntory.

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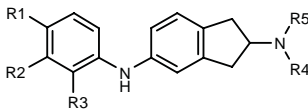
312708

2-[5-(3,4-Dichlorophenylamino)-2,3-dihydro-1H-inden-2-ylamino]-5-nitrobenzoic acid



C22 H17 Cl2 N3 O4; Mol wt: 458.2993

ACTION – An inhibitor of the aggregation of amyloid proteins, potentially useful for the treatment of Alzheimer’s disease. The compound demonstrated activity in inhibiting selfseeded amyloid fibril growth (IC₅₀ = 0.25 μM) and inhibited β-amyloid protein aggregation (IC₅₀ = 5 μM). Other specifically claimed compounds are:



Compound	R1	R2	R3	R4	R5	Formula
312709	NO2	H	CO2H	C5H11	C5H11	C ₂₆ H ₃₅ N ₃ O ₄
312710	H	H	CO2Me	H	3,4-(Cl)2-PhCH2	C ₂₄ H ₂₂ Cl ₂ N ₂ O ₂
312711	H	H	CO2H	H	3,4-(Cl)2-PhCH2	C ₂₃ H ₂₀ Cl ₂ N ₂ O ₂
312713	NO2	H	CO2H	H	3,4-(Cl)2-PhCH2	C ₂₃ H ₁₉ Cl ₂ N ₃ O ₄
312714	OMe	H	CO2H	H	3,4-(Cl)2-PhCH2	C ₂₄ H ₂₂ Cl ₂ N ₂ O ₃
312715	Me	H	CO2H	C5H11	C5H11	C ₂₇ H ₃₈ N ₂ O ₂
312716	CO2H	H	NO2	C5H11	C5H11	C ₂₆ H ₃₅ N ₃ O ₄
312717	Cl	Cl	H	H	4-NO2-2-CO2Me-Ph	C ₂₃ H ₁₉ Cl ₂ N ₃ O ₄
312718	NO2	H	CO2H	H	4-F-PhCH2	C ₂₃ H ₂₀ FN ₃ O ₄
312719	NO2	H	CO2H	4-F-PhCH2	4-F-PhCH2	C ₃₀ H ₂₅ F ₂ N ₃ O ₄
312720	NO2	H	CO2H	H	C5H11	C ₂₁ H ₂₅ N ₃ O ₄

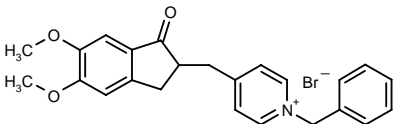
SOURCE – Pfizer.

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312787

1-Benzyl-4-(5,6-dimethoxy-1-oxo-2,3-dihydro-1*H*-inden-2-ylmethyl)pyridinium bromide



C24 H24 N O3 . Br; Mol wt: 454.3616

ACTION – A representative compound from a series of 1-benzylpyridinium salts with acetylcholinesterase-inhibitory activity. Compound was shown to inhibit acetylcholinesterase from rat brain homogenates with an IC₅₀ of 3.8 nM versus 6.7 nM for donepezil. Potentially useful for the treatment of Alzheimer’s disease, senile dementia, cerebrovascular dementia and attention deficit hyperactivity disorder.

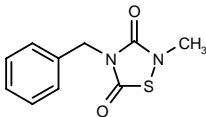
SOURCE – Eisai.

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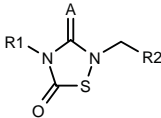
312839^{1,2}

4-Benzyl-2-methyl-1,2,4-thiadiazolidine-3,5-dione



C10 H10 N2 O2 S; Mol wt: 222.2670

ACTION – Glycogen synthase kinase-3β (GSK-3β) inhibitor (IC₅₀ = 2 μM) devoid of inhibitory activity against other kinases. Potentially useful in the treatment of Alzheimer’s disease and type 2 diabetes, as well as hyperproliferative diseases including cancer, dysplasias and metaplasias, psoriasis, arteriosclerosis and restenosis. Other exemplified thiadiazolidinone compounds are:



Compound	R1	R2	A	Formula
312840	CH2CO2Et	H	O	C ₇ H ₁₀ N ₂ O ₄ S
312842 ^{1,2}	4-MeO-Ph	H	O	C ₁₀ H ₁₀ N ₂ O ₃ S
312843 ^{1,2}	CH2Ph	Ph	S	C ₁₆ H ₁₄ N ₂ OS ₂

SOURCE – CSIC, Madrid (ES).

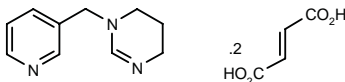
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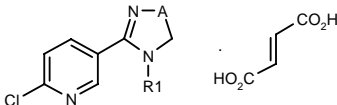
312925

1-(Pyridin-3-ylmethyl)-1,4,5,6-tetrahydropyrimidine difumarate



C10 H13 N3 . 2 C4 H4 O4; Mol wt: 407.3769

ACTION – Selective α4β2 nicotinic acetylcholine receptor agonist found to inhibit the binding of [³H]-cytisine to α4β2 receptors with a K_i of 6.9 nM, and to exhibit > 4,500-fold selectivity over α1β1γδ receptors (K_i = 32 μM); it activated α4β2 receptors expressed in *Xenopus* oocytes. Potentially useful for the treatment of Alzheimer’s disease, Parkinson’s disease, cerebrovascular dementia, Tourette’s syndrome, neurosis during cerebral infarction, anxiety and schizophrenia. Other exemplified cyclic amidine compounds are:



Compound	R1	R2	Formula
312926	H	-(CH2)2-	C ₉ H ₁₀ ClN ₃ .C ₄ H ₄ O ₄
312927	Me	-CH2-	C ₉ H ₈ ClN ₃ .C ₄ H ₄ O ₄

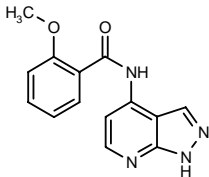
SOURCE – Suntory.

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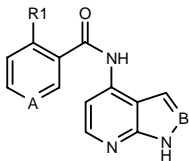
312962

2-Methoxy-*N*-(1*H*-pyrazolo[3,4-*b*]pyridin-4-yl)benzamide



C14 H12 N4 O2; Mol wt: 268.2748

ACTION – Glycogen synthase kinase-3β (GSK-3β) inhibitor (IC₅₀ = 0.12 μM) reported to inhibit β-amyloid-induced neuropathy in rat hippocampal nerve cells at 1 μM. In a rat model of cerebral ischemia, i.p. administration of compound at a dose of 30 mg/kg significantly inhibited GSK-3β. Potentially useful for the treatment of diabetes, diabetic complications, neurodegenerative diseases such as Alzheimer’s disease, AIDS encephalopathy, Huntington’s disease, Parkinson’s disease and cerebral ischemia, manic–depressive psychosis, and as an immuno-stimulant. Other exemplified aromatic amides are:



Compound	R1	A	B	Formula
312963	Cl	CH	N	C ₁₃ H ₉ ClN ₄ O
312964	i-PrO	CH	N	C ₁₆ H ₁₆ N ₄ O ₂
312965	H	N	N	C ₁₂ H ₉ N ₅ O
312966	NO2	CH	CH	C ₁₄ H ₁₀ N ₄ O ₃

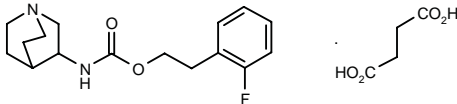
SOURCE – Mitsubishi Pharma.

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313061

N-(Quinuclidin-3-yl)carbamic acid 2-(2-fluorophenyl)ethyl ester succinate



C16 H21 F N2 O2 . C4 H6 O4; Mol wt: 410.4393

ACTION – A representative compounds from a series of azabicyclic carbamates acting as α7 nicotinic acetylcholine receptor agonists. Compound is considered to have potential in the treatment of psychotic and neurodegenerative disorders such as schizophrenia, mania, depression, anxiety, senile dementia, Alzheimer’s disease, attention deficit hyperactivity disorder, Parkinson’s disease, Huntington’s chorea, amyotrophic lateral sclerosis and multiple sclerosis.

SOURCE – Novartis.

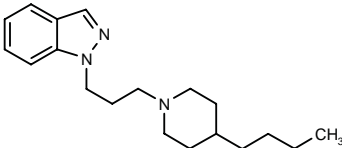
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35AKU-21

312559

1-[3-(4-Butylpiperidin-1-yl)propyl]-1*H*-indazole



C19 H29 N3; Mol wt: 299.4591

ACTION – Muscarinic M₁ and M₄ receptor agonist giving pEC₅₀ values of 7.3 and 6.5, respectively, in NIH/3T3 cells expressing M₁ and M₄ receptors, while eliciting no response in cells expressing M₂, M₃ and M₅ receptor subtypes. Compound also demonstrated intraocular pressure (IOP)-lowering activity when topically administered to glaucomatous cynomolgus monkeys. Potentially useful for the treatment of Alzheimer’s disease, cognitive impairment, glaucoma, pain and schizophrenia, among other cholinergic receptor-mediated conditions.

SOURCE – Acadia Pharmaceuticals.

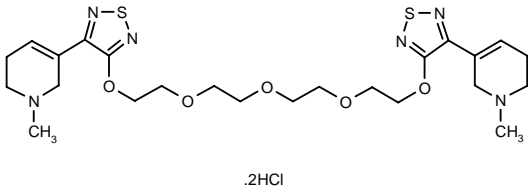
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CDD-0273-A^{1,3,4,6}

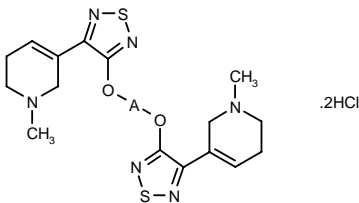
312696

3,3’-Oxybis(ethyleneoxy)bis(ethyleneoxy)bis[4-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1,2,5-thiadiazole] dihydrochloride



C24 H36 N6 O5 S2 . 2HCl; Mol wt: 625.6392

ACTION – Potent and selective muscarinic M₁ receptor agonist with subnanomolar affinity for human M₁ receptors (K_i = 0.12 nM) and strong full agonist activity at human M₁ receptors expressed in A9L cells (EC₅₀ = 8.5 nM for stimulation of phosphoinositide metabolism) and human M₄ receptors expressed in RBL-2H3 mast cells (EC₅₀ = 1.4 nM). Compound exhibited high water solubility and did not disrupt cell membranes. Potentially useful for the treatment of neurological disorders involving the cholinergic system such as Alzheimer’s disease. Other related compounds are:



Compound	A	Formula
CDD-0264-A ^{*,1,2,5,6} [292842]	-(CH2)12-	C ₂₈ H ₄₄ N ₆ O ₂ S ₂ ·2HCl
CDD-0261-A ^{1,6} [312697]	-(CH2)10-	C ₂₆ H ₄₀ N ₆ O ₂ S ₂ ·2HCl

SOURCES – University of Toledo, Toledo, OH (US); UCB Pharma.

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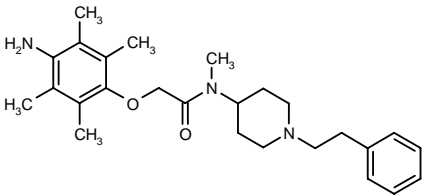
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*Identified compound **292842** Drug Data Rep 2001, 023(01): 0026.

TREATMENT OF
CEREBROVASCULAR DISEASES

312181

2-(4-Amino-2,3,5,6-tetramethylphenoxy)-N-methyl-N-[1-(2-phenylethyl)piperidin-4-yl]acetamide



C26 H37 N3 O2; Mol wt: 423.5973

ACTION – A representative compound from a series of N-piperidiny-substituted acetamides with the ability to induce the production of the Ca²⁺-binding protein calbindin D-28K, and therefore able to provide neuroprotective effects in the presence of increasing intracellular Ca²⁺ concentrations. Compound was shown to induce a 63% increase in calbindin D-28K expression in rat cerebral cortex preparations at 1 μM. At the same concentration, it was associated with a 54% survival rate in glutamate-challenged neuronal cells. In addition, at 3 mg/kg i.v. it induced 24.9% suppression of cerebral edema in rats. Potentially useful in the treatment of ischemia-associated cerebral functional disorders such as cerebral infarction,

intracerebral hemorrhage and cerebral arteriosclerosis, as well as in cerebral organic disorders including senile dementia, cerebral injury, Alzheimer's disease, Parkinson's disease and amyotrophic lateral sclerosis.

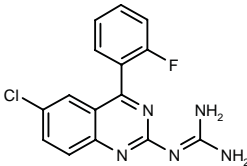
SOURCE – Suntory.

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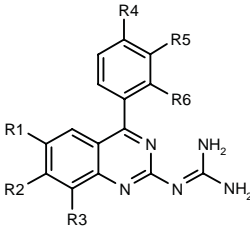
312207

N'-[6-Chloro-4-(2-fluorophenyl)quinazolin-2-yl]guanidine



C15 H11 Cl F N5; Mol wt: 315.7379

ACTION – An inhibitor of the Na⁺/H⁺ exchanger subtype 3 (NHE-3) that is reported to be useful for the treatment of thrombosis, ischemic disorders, stroke, shock states, proliferative disorders and renal disorders. Other specifically claimed 2-guanidino-4-arylquinazolines include the following:



Compound	R1	R2	R3	R4	R5	R6	Formula
312208	H	Cl	H	H	H	F	C ₁₅ H ₁₁ ClFN ₅
312209	Cl	H	H	Me	H	H	C ₁₆ H ₁₄ ClN ₅
312210	Cl	H	H	Me	Cl	H	C ₁₆ H ₁₃ Cl ₂ N ₅
312212	Cl	Me	H	Me	H	H	C ₁₇ H ₁₆ ClN ₅
312213	Cl	H	H	i-Pr	H	H	C ₁₈ H ₁₈ ClN ₅
312214	Cl	H	H	F	H	H	C ₁₅ H ₁₁ ClFN ₅
312215	Cl	H	Cl	H	H	H	C ₁₅ H ₁₁ Cl ₂ N ₅

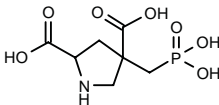
SOURCE – Merck KGaA.

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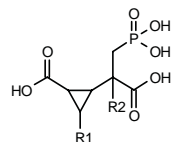
312345

4-(Phosphonomethyl)pyrrolidine-2,4-dicarboxylic acid



C7 H12 N O7 P; Mol wt: 253.1458

ACTION – A metabotropic glutamate receptor ligand with the ability to inhibit *N*-acetylated α -linked acidic dipeptidase (NAALADase). Potentially useful for the treatment of stroke, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, Huntington's disease, schizophrenia, ischemia, diabetic neuropathy, pain, anxiety, inflammation and memory impairment, as well as for treating prostate diseases and as an antiangiogenic agent. Other specifically claimed compounds are:



Compound	R1	R2	Formula
312346	H	H	C ₇ H ₁₁ O ₇ P
312347	-(CH ₂) ₂ -		C ₉ H ₁₃ O ₇ P

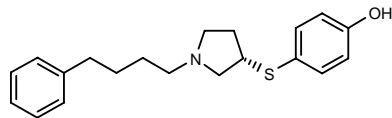
SOURCE – Guilford.

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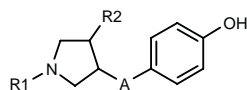
312382

4-[1-(4-Phenylbutyl)pyrrolidin-3(*S*)-ylsulfanyl]phenol



C20 H25 N O S; Mol wt: 327.4895

ACTION – NMDA receptor antagonist shown to inhibit [³H]-Ro-25-6981 binding to NMDA receptors in rat brain preparations with an IC₅₀ of 0.009 μ M. Potentially useful for the treatment of neurodegeneration associated with stroke, brain trauma and bacterial or viral infections, as well as chronic neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, Huntington's disease and amyotrophic lateral sclerosis. Other compounds from this series of pyrrolidine and piperidine derivatives are:



Compound	R1	R2	A	Isomer	Formula
312383	(CH ₂) ₄ Ph	H	S	3R	C ₂₀ H ₂₅ NOS
312384	CH ₂ CH(F)CH ₂ CH ₂ Ph	H	SO ₂	3S	C ₂₀ H ₂₄ FNO ₃ S
312386	2-OH-2-indanyl-CH ₂ CH ₂	H	SO ₂	3S	C ₂₁ H ₂₅ NO ₃ S
312387	3-(PhCH ₂)-cyclobutyl	H	SO ₂		C ₂₁ H ₂₅ NO ₃ S
312388	cis-4-Ph-cyclohexyl	H	SO ₂		C ₂₂ H ₂₇ NO ₃ S
312389	(<i>S</i>)-CH ₂ CH(F)CH ₂ CH ₂ Ph	H	(<i>R</i>)-SO	3S	C ₂₀ H ₂₄ FNO ₂ S
312392	CH ₂ CH(F)CH ₂ CH ₂ Ph	H	S	3S	C ₂₀ H ₂₄ FNOS
312393	(CH ₂) ₄ Ph	OH	SO ₂	cis	C ₂₀ H ₂₅ NO ₃ S

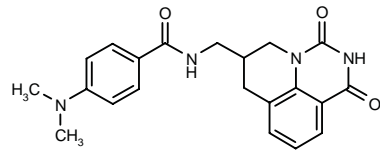
SOURCE – Roche.

REFERENCES

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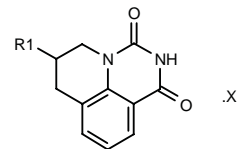
312792

4-(Dimethylamino)-*N*-(1,3-dioxo-1,2,3,5,6,7-hexahydro-pyrido[3,2,1-*ij*]quinazolin-6-ylmethyl)benzamide

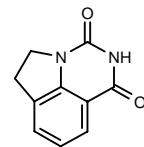


C21 H22 N4 O3; Mol wt: 378.4298

ACTION – Poly(ADP-ribose) polymerase (PARP, NAD⁺ ADP-ribosyltransferase) inhibitor (IC₅₀ < 0.005 μ M), potentially useful for the treatment of brain ischemia, neurodegenerative disorders, head and spinal cord injury, diabetes, ischemic cardiopathy, ischemia–reperfusion disorders, inflammation, cancer, cachexia, nephropathy, osteoporosis, pain, sepsis, skeletal muscle degeneration, muscular dystrophy, AIDS, etc. Other exemplified tricyclic quinazolinediones are:



Compound	R1	X	Formula
312794	H		C ₁₁ H ₁₀ N ₂ O ₂
312795	4-Pip-CONHCH ₂	HCl	C ₁₈ H ₂₂ N ₄ O ₃ .HCl



312793: C10 H8 N2 O2

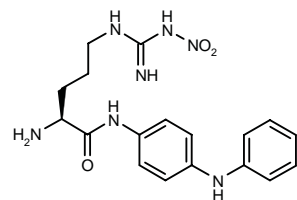
SOURCE – Sumitomo Pharmaceuticals.

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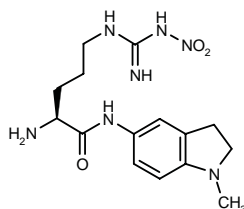
312808

N^ω-Nitro-*N*¹-[4-(phenylamino)phenyl]-L-argininamide



C18 H23 N7 O3; Mol wt: 385.4257

ACTION – Agent with the ability to inhibit neuronal and inducible nitric oxide synthase (NOS) with an $IC_{50} < 10 \mu M$ when tested for inhibition of neuronal NOS in rat cerebellum; it was found to protect cells from glutamate-induced oxidative stress with an $EC_{50} < 25 \mu M$. Potentially useful for the treatment of cerebrovascular, cardiovascular and nervous system disorders associated with oxidative stress. Another exemplified amino acid derivative is:



312809: C15 H23 N7 O3

SOURCE – SCRAS.

REFERENCES

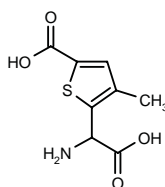
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3-MATIDA

311049

5-(1-Amino-1-carboxymethyl)-4-methylthiophene-2-carboxylic acid

2-(5-Carboxy-3-methylthien-2-yl)glycine



C8 H9 N O4 S; Mol wt: 215.2281

ACTION – Potent metabotropic glutamate $mglu_1$ receptor antagonist ($IC_{50} = 6.3 \mu M$) with high selectivity over $mglu_5$, $mglu_2$ and $mglu_4$ receptors ($IC_{50} > 300 \mu M$), as well as NMDA and AMPA receptors ($IC_{50} > 250 \mu M$). In *in vitro* models of cerebral ischemia, compound reduced the neurotoxicity induced by exposure to oxygen–glucose deprivation in mixed neuronal cell cultures (70% reduction in neuronal death) and in organotypic hippocampal slices (60% reduction in loss of pyramidal cells in the CA1 region). In *in vivo* in a rat model of focal cerebral ischemia induced by permanent occlusion of the middle cerebral artery, compound reduced the infarct volume by 40%. Potentially useful for the treatment of stroke.

SOURCE – GlaxoSmithKline.

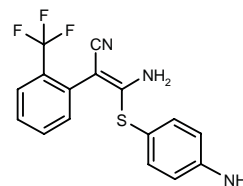
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SL-327

314820

3-Amino-3-(4-aminophenylsulfanyl)-2-[2-(trifluoromethyl)-phenyl]prop-2-enenitrile



C16 H12 F3 N3 S; Mol wt: 335.3518

ACTION – Selective MEK1/2 protein kinase inhibitor able to dose-dependently (10-100 mg/kg i.p.) block ERK kinase phosphorylation in both controls and mice subjected to ischemia/reperfusion; reductions in infarct size of 63.6 and 50.7% (compared to vehicle-treated animals) were obtained with the highest dose given before and after ischemia, respectively. Mice treated with compound also showed improvement in neurological deficits. The inhibition of MEK kinases was associated with expression of c-fos, zif268, MMP-9, IL-11 and IL-1 β genes, as well as downregulation of active caspase 3 and apoptosis. Potentially useful for the treatment of stroke.

SOURCE – Bristol-Myers Squibb.

REFERENCES

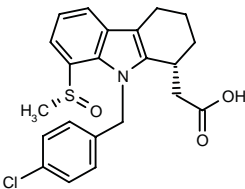
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RESPIRATORY DRUGS

TREATMENT OF UPPER
RESPIRATORY TRACT DISORDERS

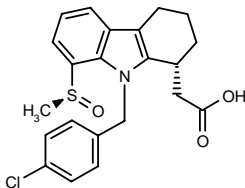
312177

2-[9-(4-Chlorobenzyl)-8-[S(R)-methylsulfinyl]-2,3,4,9-tetrahydro-1H-carbazol-1(R)-yl]acetic acid



C22 H22 Cl N O3 S; Mol wt: 415.9388

ACTION – Prostaglandin D₂ (DP) receptor antagonist (K_i = 1.7 nM), potentially useful for the treatment of allergic rhinitis and other allergic conditions. Another exemplified tetrahydrocarbazole-1-acetic acid is:



312178: C22 H22 Cl N O3 S

SOURCE – Merck Frosst.

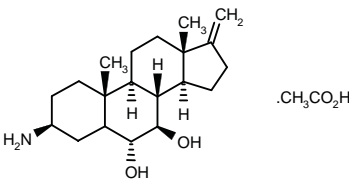
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ASTHMA THERAPY

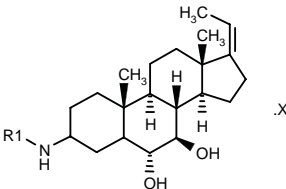
312562

3β-Amino-17-methyleneandrostane-6α,7β-diol acetate



C20 H33 N O2 . C2 H4 O2; Mol wt: 379.5373

ACTION – Antiinflammatory steroid reported to produce 57, 60 and 64% inhibition of the accumulation of eosinophils, neutrophils and lymphocytes, respectively, in lung lavage fluid of ovalbumin-sensitized rats at an oral dose of 5 mg/kg/day for 4 days. Potentially useful for the treatment of asthma, allergy, chronic obstructive pulmonary disease, atopic dermatitis, solid tumors, AIDS, ischemia–reperfusion injury and cardiac arrhythmia. Other exemplified compounds are:



Compound	R1	Isomer	X	Formula
312563	H	3β	acetate	C ₂₁ H ₃₅ NO ₂ ·C ₂ H ₄ O ₂
312564	cyclopentyl		acetate	C ₂₆ H ₄₃ NO ₂ ·C ₂ H ₄ O ₂
312565	CH ₂ CH ₂ NHPr		2HCl	C ₂₆ H ₄₆ N ₂ O ₂ ·2HCl

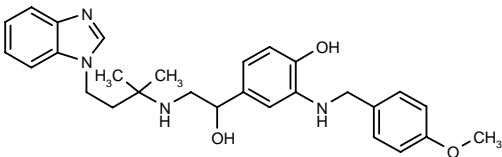
SOURCE – InflaZyme.

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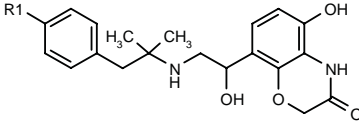
312611

4-[2-[3-(1H-Benzimidazol-1-yl)-1,1-dimethylpropylamino]-1-hydroxyethyl]-2-(4-methoxybenzylamino)phenol



C28 H34 N4 O3; Mol wt: 474.6016

ACTION – A slow-acting β-adrenergic agent, potentially useful for the treatment of bronchial asthma and other inflammatory diseases. Other specifically claimed compounds are:



Compound	R1	Formula
312612	N(Me)2	C ₂₂ H ₂₉ N ₃ O ₄
312613	OBu	C ₂₄ H ₃₂ N ₂ O ₅

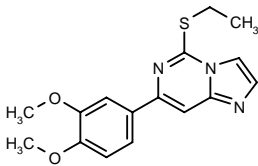
SOURCE – Boehringer Ingelheim.

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312652

7-(3,4-Dimethoxyphenyl)-5-(ethylsulfanyl)imidazo[1,2-*c*]-pyrimidine



C16 H17 N3 O2 S; Mol wt: 315.3953

ACTION – A representative compound from a series of imidazo- and triazolopyrimidine derivatives that inhibit Syk tyrosine kinase. The compound demonstrated strong activity in an anaphylactic bronchoconstriction test in rats when administered at 3 mg/kg i.v. 5 min before challenge. Potentially useful for the treatment of allergic diseases such as asthma, allergic rhinitis, atopic dermatitis and conjunctivitis, among others.

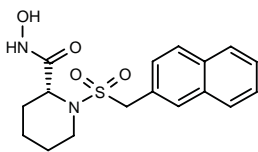
SOURCE – Bayer.

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1. Yura, T. et al. (Bayer AG) *Imidazopyrimidine derivs. and triazolopyrimidine derivs.* JP 2001302667, WO 0183485.

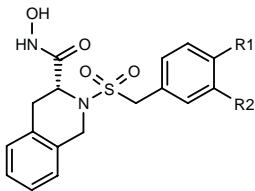
313027

1-(Naphthalen-2-ylmethylsulfonyl)piperidine-2(*R*)-carboxylic acid

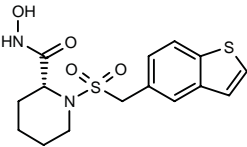


C17 H20 N2 O4 S; Mol wt: 348.4210

ACTION – Agent with the ability to inhibit the formation of soluble human CD23 ($IC_{50} < 1 \mu M$) and the processing of TNF, while being devoid of collagenase-inhibitory effect. Potentially useful for the treatment of allergy, asthma, atopic dermatitis, inflammatory disorders including Alzheimer's disease and multiple sclerosis, and autoimmune diseases. Other specifically claimed *N*-sulfonyl-hydroxamic acid derivatives are:



Compound	R1,R2	Formula
313030	-CH=CHCH=CH-	C ₂₁ H ₂₀ N ₂ O ₄ S
313031	-SCH=CH-	C ₁₉ H ₁₈ N ₂ O ₄ S ₂



313028: C15 H18 N2 O4 S2

SOURCE – GlaxoSmithKline.

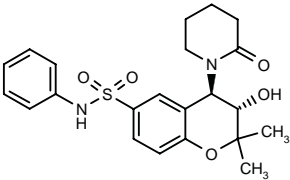
REFERENCES

1. Bruton, G. and Orlek, B.S. (GlaxoSmithKline plc) *N-Sulfonyl hydroxamic acid derivs. as inhibitors of CD23.* WO 0185721.

KCO-912

280588

(3*S*,4*R*)-3-Hydroxy-2,2-dimethyl-4-(2-oxopiperidin-1-yl)-*N*-phenyl-1-benzopyran-6-sulfonamide



C22 H26 N2 O5 S; Mol wt: 430.5224

ACTION – Potassium channel opener with high affinity for K_{ATP} channels ($pK_i = 8.28$ and 7.96 , respectively, for inhibition of [3H]-P-1075 and [3H]-glibenclamide binding in rat aortic strips), able to induce $^{86}Rb^+$ efflux from rat aortic rings with a pEC_{50} of 7.51 . In guinea pigs, compound given intratracheally reduced airways hyperactivity induced by ozone or immune complexes ($ED_{50} = 1$ and $0.03 \mu g/kg$, respectively), and in spontaneously hyper-reactive monkeys, compound given by inhalation reversed methacholine-induced bronchoconstriction with an ED_{50} of $1.2 \mu g/kg$. No effect on blood pressure or heart rate was seen in guinea pigs or monkeys at doses of $> 100 \mu g/kg$. A promising candidate for the treatment of asthma.

SOURCE – Novartis.

REFERENCES

1. Manley, P.W. (Novartis AG;Novartis Deutschland GmbH) *Benzopyrans and pharmaceutical compsns. containing them.* EP 0828733, JP 1999505820, US 5905156, WO 9637490.

2. Buchheit, K.-H. et al. *KCO912: A potent and selective opener of ATP-dependent potassium (K_{ATP}) channels with selectivity for the airways.* Br J Pharmacol 2001, 134(Suppl.): Abst 69P.

3. Buchheit, K.-H. et al. *KCO912: A potent and selective opener of ATP-dependent potassium (K_{ATP}) channels with selectivity for the airways.* Br J Pharmacol 2001, 134(Suppl.): Abst 70P.

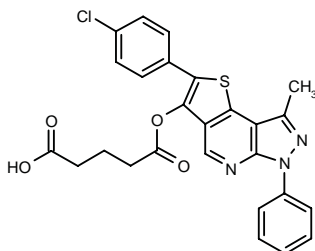
4. Reinhardt, J. *Innovation and productivity drive sustained growth.* Novartis R&D Invest Semin (Dec 6, Basel) 2000.

5. *Novartis R&D day 1999: Innovation drives future growth.* DailyDrugNews.com (Daily Essentials) 1999, Sept 24.

LASSBIO-341

277679

5-[2-(4-Chlorophenyl)-8-methyl-6-phenyl-6*H*-pyrazolo-[3,4-*b*]thieno[2,3-*d*]pyridin-3-yloxy]-5-oxopentanoic acid



C₂₆ H₂₀ Cl N₃ O₄ S; Mol wt: 505.9800

ACTION – Dual thromboxane synthetase inhibitor and leukotriene LTD₄ receptor antagonist proven to selectively inhibit LTD₄-induced contractions of isolated guinea pig trachea (IC₅₀ = 43.7 μM) and to completely inhibit arachidonic acid- and collagen-induced rabbit platelet aggregation at a concentration of 100 μM. In the rat carrageenan-induced pleurisy model it was more effective than indomethacin in inhibiting inflammatory cell infiltration (36.2% at 100 μmol/kg p.o.) and exudation. Potentially useful as an antiasthmatic agent.

SOURCE – Universidade Federal do Rio de Janeiro, Rio de Janeiro (BR).

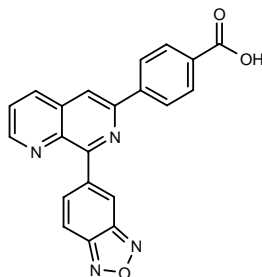
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- Cardoso, C.R. et al. *Design, synthesis and pharmacological evaluation of novel pyrazolo[3,4-*b*]thieno[2,3-*d*]pyridine acid derivatives: A new class of anti-inflammatory and anti-platelet agents*. Bioorg Med Chem Lett 2002, 12(1): 9.
- Silva, K.C.M. et al. *Pharmacological profile of new thienopyrazole-pyridine derivatives with anti-platelet and anti-inflammatory effects*. Mediators Inflamm 1999, 8(Suppl. 1): Abst P-11-38.

NVP-ABE-171

313083

4-[8-(2,1,3-Benzoxadiazol-5-yl)-1,7-naphthyridin-6-yl]-benzoic acid



C₂₁ H₁₂ N₄ O₃; Mol wt: 368.3508

ACTION – Phosphodiesterase type 4 (PDE4) inhibitor active against all purified human PDE4 isotypes (PDE4A, PDE4B, PDE4C and PDE4D; IC₅₀ = 602, 34, 1230 and 1.5 nM, respectively) and inactive against PDE1, PDE2, PDE3 and PDE5 (IC₅₀ > 10,000 nM); compound was not selective in terms of affinity for the [³H]-rolipram binding site (IC₅₀ = 1 nM). It strongly inhibited lipopolysaccharide (LPS)/interferon gamma-stimulated TNF-α release from

human peripheral blood mononuclear cells with an IC₅₀ of 68 nM. *In vivo* in a rat model of adjuvant-induced arthritis, a dose of 5 mg/kg b.i.d. p.o. inhibited paw swelling by 50%. In a murine model of lung inflammation induced by intranasal LPS challenge, compound inhibited both neutrophilia and TNF-α levels in bronchoalveolar lavage fluid (BALF) by 94 and 45%, respectively, at an oral dose of 10 mg/kg. In a rat model of lung inflammation induced by antigen challenge in sensitized animals, it inhibited eosinophil number and eosinophil peroxidase activity in the BALF by over 90% at 1 mg/kg. For comparison, Arfilo® had no effect in the LPS-challenged mouse model even at the highest dose of 10 mg/kg, and it was less potent than compound in rats challenged with antigen. Potentially useful for the treatment of inflammatory lung diseases such as asthma and chronic obstructive pulmonary disease.

SOURCE – Novartis.

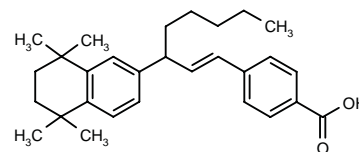
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- Hersperger, R. (Novartis AG) *Naphthyridine derivs*. EP 0934320, JP 2001502717, US 6136821, WO 9818796.
- Hersperger, R. et al. *Synthesis of 4-(8-benzo[1,2,5]oxadiazol-5-yl-[1,7]naphthyridine-6-yl)-benzoic acid: A potent and selective phosphodiesterase type 4D inhibitor*. Bioorg Med Chem Lett 2002, 12(2): 233.
- Trifilieff, A. et al. *Effect of a novel PDE4 inhibitor, NVP-ABE171, a 1,7-naphthyridine derivative in models of lung inflammation in mice and rats*. Br J Pharmacol 2001, 134(Suppl.): Abst 68P.

TREATMENT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASES

312722

4-[3-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)-1(*E*)-octenyl]benzoic acid



C₂₉ H₃₈ O₂; Mol wt: 418.6172

ACTION – A selective retinoic acid receptor RARγ agonist, potentially useful for the treatment of emphysema and related pulmonary disorders. Compound exhibited 32, 49 and 53% of alveolar repair area at 0.03, 0.01 and 0.003 mg/kg p.o., respectively, in a model of elastase-induced emphysema in rats.

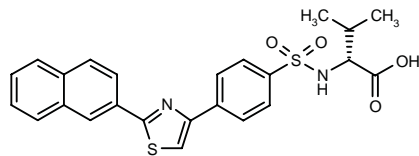
SOURCE – Roche.

REFERENCES

- Belloni, P.N. et al. (F. Hoffmann-La Roche AG) *New gamma selective retinoids*. WO 0183438.

312992

N-[4-[2-(2-Naphthyl)thiazol-4-yl]phenylsulfonyl]-D-valine



C24 H22 N2 O4 S2; Mol wt: 466.5798

ACTION – Matrix metalloproteinase MMP-12 (metallo-elastase) inhibitor (IC_{50} = 0.037 μ M) with the ability to increase maximum inspiratory capacity in rats under systemic exposure to tobacco. Potentially useful for the treatment of chronic obstructive pulmonary disease, osteoarthritis, rheumatoid arthritis, corneal ulcer, periodontitis, viral infection, atherosclerosis, restenosis, sepsis, coronary thrombosis, multiple sclerosis, retinopathy, etc.

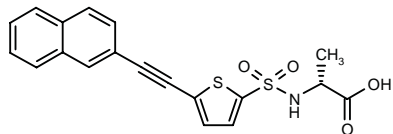
SOURCE – Shionogi.

REFERENCES

1. Furue, S. et al. (Shionogi & Co. Ltd.) *Thiazole and oxazole derivs.* WO 0183461.

312993

N-[5-(2-Naphthylethynyl)thien-2-ylsulfonyl]-D-alanine



C19 H15 N O4 S2; Mol wt: 385.4625

ACTION – Matrix metalloproteinase MMP-12 (metallo-elastase) inhibitor (IC_{50} = 0.023 μ M) with the ability to increase maximum inspiratory capacity in rats under systemic exposure to tobacco. Potentially useful for the treatment of chronic obstructive pulmonary disease, osteoarthritis, rheumatoid arthritis, corneal ulcer, periodontitis, viral infection, atherosclerosis, restenosis, sepsis, coronary thrombosis, multiple sclerosis and retinopathy, among other conditions.

SOURCE – Shionogi.

REFERENCES

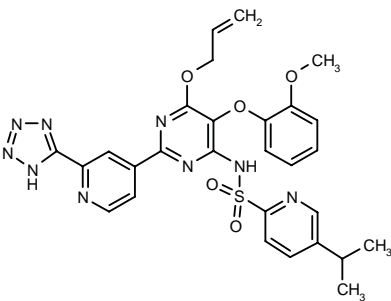
1. Hori, Y. et al. (Shionogi & Co. Ltd.) *MMP-12 inhibitors.* WO 0183431.

CARDIOVASCULAR DRUGS

ANTIHYPERTENSIVE DRUGS

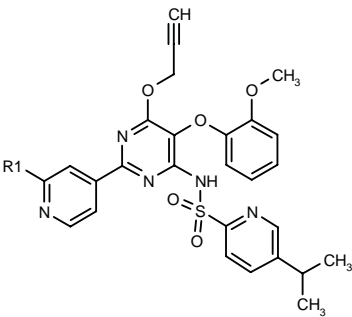
312334

N-[6-(Allyloxy)-5-(2-methoxyphenoxy)-2-[2-(1H-tetrazol-5-yl)pyridin-4-yl]pyrimidin-4-yl]pyrimidin-4-yl]-5-isopropylpyridine-2-sulfonamide



C28 H27 N9 O5 S; Mol wt: 601.6453

ACTION – Endothelin antagonist with the ability to inhibit endothelin binding to membranes from CHO cells expressing ET_A or ET_B receptors, with respective IC_{50} values of 13.9 and 115 nM. It was also tested for inhibition of endothelin-induced contractions in isolated rat aorta rings (ET_A receptors), giving a pA_2 of 7.58. Potentially useful for the treatment of endothelin-related disorders including hypertension, ischemia, vasospasm, angina pectoris, migraine, asthma and inflammatory or proliferative disorders. Other exemplified sulfonamido-pyrimidines are:



Compound	R1	Formula
312337	5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl	C ₂₈ H ₂₆ N ₇ O ₇ S
312338	CONH2	C ₂₈ H ₂₆ N ₆ O ₆ S

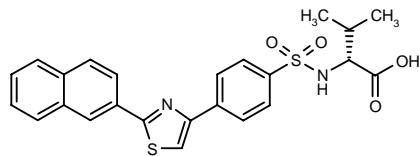
SOURCE – Actelion.

REFERENCES

1. Bolli, M. et al. (Actelion Ltd.) *Pyrimidine-sulfonamides having endothelin-antagonist activity.* WO 0181335.

312992

N-[4-[2-(2-Naphthyl)thiazol-4-yl]phenylsulfonyl]-D-valine



C24 H22 N2 O4 S2; Mol wt: 466.5798

ACTION – Matrix metalloproteinase MMP-12 (metallo-elastase) inhibitor (IC_{50} = 0.037 μ M) with the ability to increase maximum inspiratory capacity in rats under systemic exposure to tobacco. Potentially useful for the treatment of chronic obstructive pulmonary disease, osteoarthritis, rheumatoid arthritis, corneal ulcer, periodontitis, viral infection, atherosclerosis, restenosis, sepsis, coronary thrombosis, multiple sclerosis, retinopathy, etc.

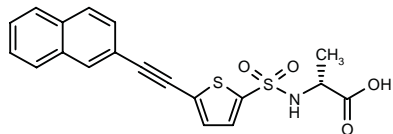
SOURCE – Shionogi.

REFERENCES

1. Furue, S. et al. (Shionogi & Co. Ltd.) *Thiazole and oxazole derivs.* WO 0183461.

312993

N-[5-(2-Naphthylethynyl)thien-2-ylsulfonyl]-D-alanine



C19 H15 N O4 S2; Mol wt: 385.4625

ACTION – Matrix metalloproteinase MMP-12 (metallo-elastase) inhibitor (IC_{50} = 0.023 μ M) with the ability to increase maximum inspiratory capacity in rats under systemic exposure to tobacco. Potentially useful for the treatment of chronic obstructive pulmonary disease, osteoarthritis, rheumatoid arthritis, corneal ulcer, periodontitis, viral infection, atherosclerosis, restenosis, sepsis, coronary thrombosis, multiple sclerosis and retinopathy, among other conditions.

SOURCE – Shionogi.

REFERENCES

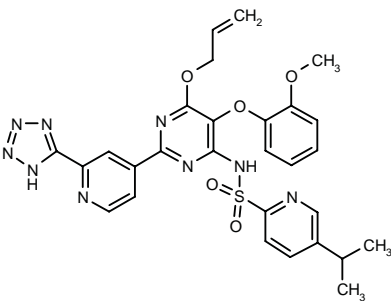
1. Hori, Y. et al. (Shionogi & Co. Ltd.) *MMP-12 inhibitors.* WO 0183431.

CARDIOVASCULAR DRUGS

ANTIHYPERTENSIVE DRUGS

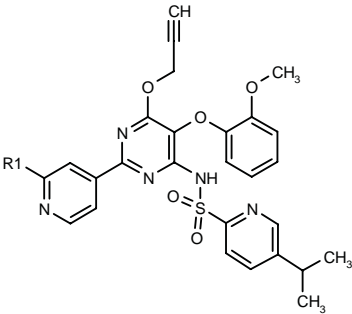
312334

N-[6-(Allyloxy)-5-(2-methoxyphenoxy)-2-[2-(1H-tetrazol-5-yl)pyridin-4-yl]pyrimidin-4-yl]pyrimidin-4-yl]-5-isopropylpyridine-2-sulfonamide



C28 H27 N9 O5 S; Mol wt: 601.6453

ACTION – Endothelin antagonist with the ability to inhibit endothelin binding to membranes from CHO cells expressing ET_A or ET_B receptors, with respective IC_{50} values of 13.9 and 115 nM. It was also tested for inhibition of endothelin-induced contractions in isolated rat aorta rings (ET_A receptors), giving a pA_2 of 7.58. Potentially useful for the treatment of endothelin-related disorders including hypertension, ischemia, vasospasm, angina pectoris, migraine, asthma and inflammatory or proliferative disorders. Other exemplified sulfonamido-pyrimidines are:



Compound	R1	Formula
312337	5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl	C ₂₈ H ₂₆ N ₇ O ₇ S
312338	CONH2	C ₂₈ H ₂₆ N ₆ O ₆ S

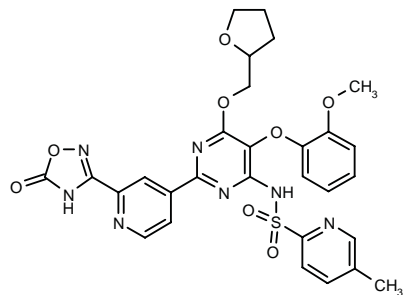
SOURCE – Actelion.

REFERENCES

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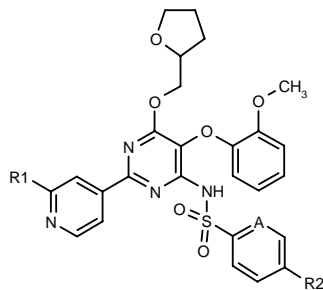
312340

N-[5-(2-Methoxyphenoxy)-2-[2-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)pyridin-4-yl]-6-(tetrahydrofuran-2-ylmethoxy)pyrimidin-4-yl]-5-methylpyridine-2-sulfonamide



C29 H27 N7 O8 S; Mol wt: 633.6393

ACTION – Endothelin antagonist with the ability to inhibit endothelin binding to membranes from CHO cells expressing ET_A or ET_B receptors, with respective IC₅₀ values of 16 and 1280 nM. It was also tested for inhibition of endothelin-induced contractions in isolated rat aorta rings (ET_A receptors), giving a pA₂ of 7.58. Potentially useful for the treatment of endothelin-related disorders including hypertension, ischemia, vasospasm, angina pectoris, migraine, asthma and inflammatory or proliferative disorders. Other exemplified sulfonamido-pyrimidines are:



Compound	R1	R2	A	Formula
312341	H	i-Pr	N	C ₂₉ H ₃₁ N ₅ O ₆ S
312342	5-tetrazolyl	i-Pr	N	C ₃₀ H ₃₁ N ₉ O ₆ S
312343	H	t-Bu	CH	C ₃₁ H ₃₄ N ₄ O ₆ S
312344	5-thiooxo-4,5-dihydro-1,2,4-oxadiazol-3-yl	Me	N	C ₂₉ H ₂₇ N ₇ O ₇ S ₂

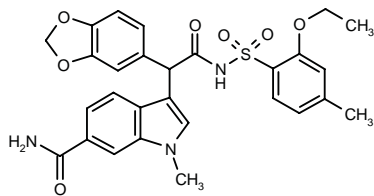
SOURCE – Actelion.

REFERENCES

1. Boss, C. et al. (Actelion Ltd.) *Substd. sulfonylaminopyrimidines*. WO 0181338.

314228

3-[1-(1,3-Benzodioxol-5-yl)-1-[*N*-(2-ethoxy-4-methylphenylsulfonyl)carbamoyl]methyl]-1-methyl-1*H*-indole-6-carboxamide



C28 H27 N3 O7 S; Mol wt: 549.6013

ACTION – Nonpeptide endothelin ET_A receptor antagonist with subnanomolar binding affinity for ET_A receptors (IC₅₀ = 0.55 nM) and high selectivity over ET_B receptors (IC₅₀ = 397 nM). Potentially useful for the treatment of hypertension.

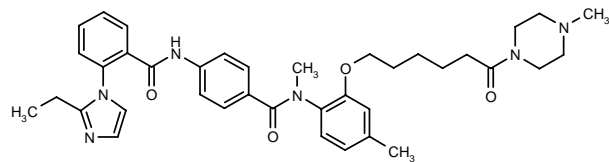
SOURCE – Pfizer.

REFERENCES

1. Rawson, D.J. et al. *The design and synthesis of a novel series of indole derived selective ET_A antagonists*. Bioorg Med Chem Lett 2002, 12(2): 125.

314250

2-(2-Ethyl-1*H*-imidazol-1-yl)-*N*-[4-[*N*-methyl-*N*-[4-methyl-2-[6-(4-methylpiperazin-1-yl)-6-oxohexyloxy]phenyl]-carbamoyl]phenyl]benzamide



C38 H46 N6 O4; Mol wt: 650.8194

ACTION – High-affinity ligand for the arginine vasopressin (AVP) V_{1a} receptor (K_i = 5.71 nM) with 140-fold selectivity over V₂ receptors (K_i = 782 nM), able to antagonize *in vivo* the blood pressure response induced by AVP in pithed rats with an ID₅₀ value of 0.008 mg/kg i.v. Potentially useful for the treatment of hypertension.

SOURCE – Yamanouchi.

REFERENCES

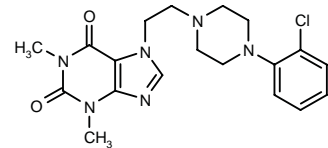
1. Kakefuda, A. et al. *N-Methylbenzanilide derivatives as a novel class of selective V_{1a} receptor antagonists*. Bioorg Med Chem Lett 2002, 12(2): 229.

KMUP-1

311088

7-[2-[4-(2-Chlorophenyl)piperazin-1-yl]ethyl]-1,3-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione

7-[2-[4-(2-Chlorophenyl)piperazin-1-yl]ethyl]theophylline



C19 H23 Cl N6 O2; Mol wt: 402.8837

ACTION – Xanthine derivative that combines K⁺ channel-opening, phosphodiesterase-inhibiting and soluble guanylyl cyclase-stimulating activities. *In vitro*, compound induced vasorelaxation in intact or denuded aortic rings precontracted with phenylephrine; this vasorelaxation was reduced by the removal of the epithelium, the presence of the nitric oxide synthase inhibitor L-NAME or pretreatment with various K⁺ channel blockers. In anesthetized rats, compound produced dose-dependent (1-5 mg/kg i.v.) and sustained hypotension and a short-acting bradycardic effect. Potentially useful for the treatment of hypertension.

SOURCE – Kaohsiung Medical College, Kaohsiung (TW).

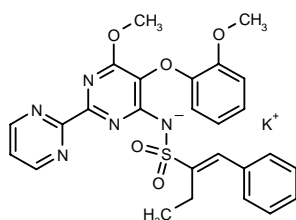
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1. Wu, B.-N. et al. A xanthine-based KMUP-1 with cyclic GMP enhancing and K⁺ channels opening activities in rat aortic smooth muscle. *Br J Pharmacol* 2001, 134(2): 265.

YM-91746

313097

N-[6-Methoxy-5-(2-methoxyphenoxy)-2,2'-bipyrimidin-4-yl]-1-phenyl-1(*E*)-butene-2-sulfonamide potassium salt



C26 H24 K N5 O5 S; Mol wt: 557.6696

ACTION – Endothelin ET_A receptor antagonist with high binding affinity for the human ET_A receptor (IC₅₀ = 3.3 nM) and high selectivity relative to the ET_B receptor (IC₅₀ = 790 nM). Compound exhibited potent oral activity in inhibiting the pressor response to big ET-1 in anesthetized pithed rats (ID₅₀ = 1.7 mg/kg), as well as in conscious rats (52% at 0.3 mg/kg). Potentially useful for the treatment of hypertension.

SOURCE – Yamanouchi.

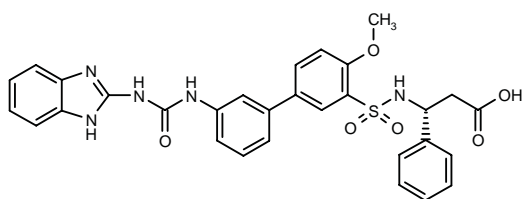
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1. Harada, H. et al. (Yamanouchi Pharmaceutical Co., Ltd.) Arylethanesulfonamide derivs. and drug compsn. containing the same. EP 0882719, US 6083955, WO 9722595.
2. Harada, H. et al. Synthesis and structure-activity relationships in a series of ethenesulfonamide derivatives, a novel class of endothelin receptor antagonists. *Chem Pharm Bull* 2001, 49(12): 1593.

TREATMENT OF DISORDERS OF THE CORONARY ARTERIES AND ATHEROSCLEROSIS

314238

3(*R*)-[3'-[3-(1*H*-Benzimidazol-2-yl)ureido]-4-methoxybiphenyl-3-ylsulfonamido]-3-phenylpropionic acid



C30 H27 N5 O6 S; Mol wt: 585.6383

ACTION – Peptidomimetic integrin α_vβ₃ (vitronectin) receptor antagonist (IC₅₀ = 30 nM for inhibition of platelet-derived growth factor [PDGF]-induced human aorta smooth muscle cell migration) with high selectivity for the α_vβ₃ receptor over the platelet gpIIb/IIIa receptor (K_i = 0.7 and 300 nM, respectively). Potentially useful for the treatment of restenosis.

SOURCE – Bayer.

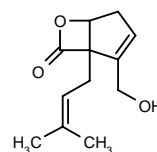
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2. Urbahns, K. et al. Biphenyls as potent vitronectin receptor antagonists. *Bioorg Med Chem Lett* 2002, 12(2): 205.

PERCYQUINNIN

310612

2-(Hydroxymethyl)-1-(3-methyl-2-butenyl)-6-oxabicyclo-[3.2.0]hept-2-en-7-one



C12 H16 O3; Mol wt: 208.2554

ACTION – Lipase inhibitor isolated from cultures of the basidiomycete *Stereum complicatum* ST 001837 (DSM 13303), shown to inhibit lipase purified from rat adipocytes with an IC₅₀ value of 2 μM. Compound is expected to be useful for the treatment of hyperlipidemia-related disorders such as atherosclerosis, hypertension and diabetes.

SOURCE – Aventis Pharma.

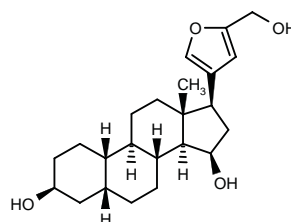
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ANTIARRHYTHMIC DRUGS

312183

17β-[5-(Hydroxymethyl)furan-3-yl]-5β-estrane-3β,15β-diol



C23 H34 O4; Mol wt: 374.5176

ACTION – A representative compound from a series of 19-norbufalin derivatives with Na⁺/K⁺-ATPase-inhibitory activity, proven to induce an increase in cardiac contractility when tested in guinea pigs. Potentially useful for the treatment of cardiac, renal and proliferative diseases including arrhythmia, heart failure, diuresis, etc.

SOURCE – Yissum.

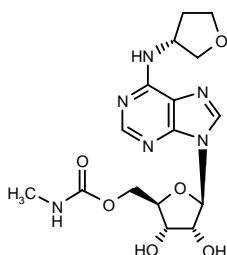
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CVT-2759

306259

5'-O-(N-Methylcarbamoyl)-N⁶-[tetrahydrofuran-3(R)-yl]-adenosine



C16 H22 N6 O6; Mol wt: 394.3858

ACTION – Adenosine A₁ receptor partial agonist proven to partially reverse the effect of N⁶-cyclopentyladenosine (CPA) or adenosine on the S-H interval prolongation in isolated guinea pig hearts. In A₁ receptor-rich tissues such as FRTL-5 cells and rat epididymal adipocytes, compound exhibited full agonist activity (EC₅₀ = 74 and 35 nM, respectively, for inhibition of forskolin-induced cAMP production). In guinea pig isolated hearts compound increased the S-H interval (EC₅₀ = 3.1 μM) without causing second-degree atrioventricular block; it increased coronary conductance and it significantly inhibited isoproterenol-induced arrhythmic activity (at 10 μM) without reducing the amplitude of twitch shortening and L-type Ca²⁺ currents. Potentially useful for the treatment of cardiac arrhythmias.

SOURCE – CV Therapeutics.

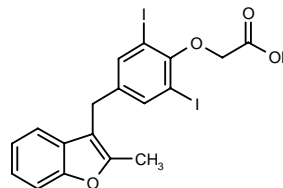
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KB-130015

279038

2-[2,6-Diiodo-4-(2-methyl-1-benzofuran-3-ylmethyl)-phenoxy]acetic acid



C18 H14 I2 O4; Mol wt: 548.1046

ACTION – Class III antiarrhythmic agent, a benzofuran benzyl derivative with high affinity for human thyroid hormone receptors hThR α₁ and hThR β₁ (IC₅₀ = 4.5 and 5.1 μM, respectively) and functional antagonist activity at these receptors (IC₅₀ = 2.2 and 4.1 μM, respectively, in a reporter cell assay in CHO cells stably transfected with hThRα₁ and hThRβ₁, respectively). Transmembrane electrophysiological experiments in guinea pig papillary muscle showed that compound at a dose of 40 mg/kg/day i.p. for 20 days prolonged the action potential duration at 50% and 90% repolarization (ADP₅₀ and ADP₉₀) in the absence of reverse rate dependency. In rats after chronic oral administration, the effects of compound on lipid metabolism and liver function appeared to be less severe than those of amiodarone, without producing the reduction in weight gain seen with amiodarone.

SOURCE – Karo Bio.

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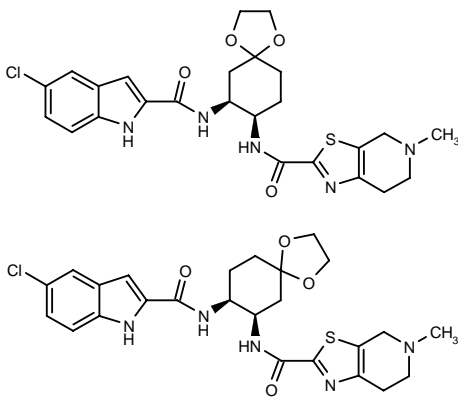
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AGENTS AFFECTING BLOOD COAGULATION

ANTICOAGULANTS

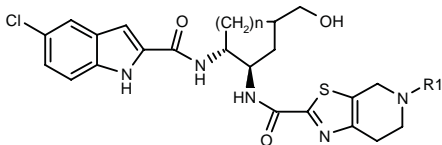
311666

Mixture of (±)-*cis*-*N*-[7-(5-chloro-1*H*-indol-2-ylcarbox-amido)-1,4-dioxaspiro[4.5]dec-8-yl]-5-methyl-4,5,6,7-tetrahydro-thiazolo[5,4-*c*]pyridine-2-carboxamide and (±)-*cis*-*N*-[8-(5-chloro-1*H*-indol-2-ylcarboxamido)-1,4-dioxaspiro[4.5]dec-7-yl]-5-methyl-4,5,6,7-tetrahydrothiazolo-[5,4-*c*]pyridine-2-carboxamide

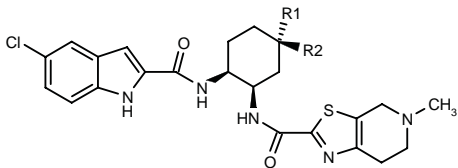


C25 H28 Cl N5 O4 S; Mol wt: 530.0460

ACTION – Anticoagulant with an IC₅₀ of 1.4 nM against human factor Xa, useful for the treatment of thrombosis and embolism. Other exemplified ethylenediamine derivatives are:



Compound	R1	n	Isomer	Formula
311669	i-Pr	1	racemic	C ₂₅ H ₃₀ ClN ₅ O ₃ S
311670	C(Me)2CH2OH	1	racemic	C ₂₆ H ₃₂ ClN ₅ O ₄ S
311676	Me	2	1R,2R,5S	C ₂₄ H ₂₆ ClN ₅ O ₃ S



Compound	R1	R2	Formula
311671	H	CO2Me	C ₂₅ H ₂₈ ClN ₅ O ₄ S
311673	CONHEt	H	C ₂₆ H ₃₁ ClN ₆ O ₃ S
311675	CON(Me)2	H	C ₂₆ H ₃₁ ClN ₆ O ₃ S

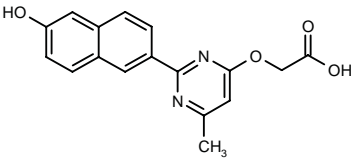
SOURCE – Daiichi Pharmaceutical.

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311793

2-[2-(6-Hydroxynaphthalen-2-yl)-6-methylpyrimidin-4-yl]oxy]acetic acid



C17 H14 N2 O4; Mol wt: 310.3076

ACTION – A representative compound from a series of naphthalene derivatives with fibrinolysis-accelerating activity, potentially useful as antithrombotic agents. Compound was found to promote plasmin formation *in vitro* and protected mice against thrombin-induced pulmonary thrombosis, with survival rates of 70 and 80% at 0.1 mg/kg p.o. and i.v., respectively.

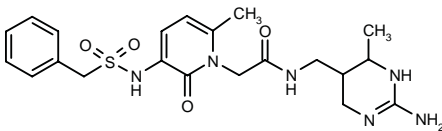
SOURCE – Torii.

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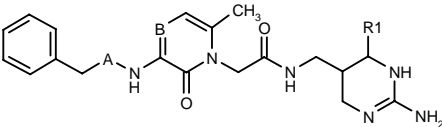
312156

N-(2-Amino-6-methyl-1,4,5,6-tetrahydropyrimidin-5-yl-methyl)-2-[3-(benzylsulfonamido)-6-methyl-2-oxo-1,2-dihydropyridin-1-yl]acetamide



C21 H28 N6 O4 S; Mol wt: 460.5562

ACTION – Anticoagulant, a thrombin inhibitor with high specificity for α-thrombin compared to other serine proteases, giving an IC₅₀ of 100 nM or less when tested for α-thrombin inhibition while being inactive in trypsin and factor Xa assays. Other exemplified compounds from this series of pyrazinone and pyridone derivatives are:



Compound	R1	A	B	Formula
312157	Me	CH2	N	C ₂₁ H ₂₉ N ₇ O ₂
312158	H	SO2	CH	C ₂₀ H ₂₆ N ₆ O ₄ S
312159	H	CH2	N	C ₂₀ H ₂₇ N ₇ O ₂

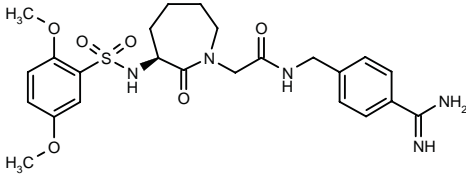
SOURCE – Corvas.

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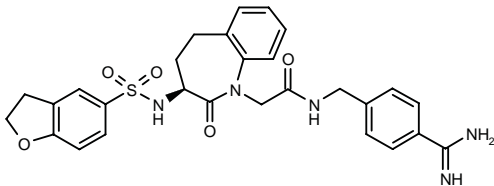
312160

N-(4-Amidinobenzyl)-2-[3(S)-(2,5-dimethoxyphenyl)sulfonamido]-2-oxoperhydroazepin-1-yl]acetamide



C24 H31 N5 O6 S; Mol wt: 517.6039

ACTION – Anticoagulant, a thrombin inhibitor with high specificity for α-thrombin compared to other serine proteases, giving an IC₅₀ of 100 nM or less when tested for α-thrombin inhibition versus 2500 nM or more in trypsin and factor Xa assays. Another exemplified compound from this series of tetrahydroazepinone derivatives is:



312161: C28 H29 N5 O5 S

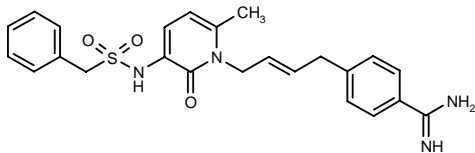
SOURCE – Corvas.

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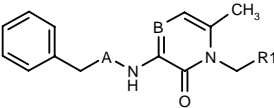
312162

4-[4-[3-(Benzylsulfonamido)-6-methyl-2-oxo-1,2-dihydro-pyridin-1-yl]-2-butenyl]benzamidine



C24 H26 N4 O3 S; Mol wt: 450.5604

ACTION – Anticoagulant, a thrombin inhibitor with high specificity for α-thrombin compared to other serine proteases, giving an IC₅₀ of 100 nM or less when tested for α-thrombin inhibition versus 2500 nM or more in trypsin and factor Xa assays. Other exemplified compounds from this series of pyrazinone and pyridinone derivatives are:



Compound	R1	A	B	Formula
312164	trans-2-[4-[NH2C(=NH)]-PhCH2]- -cyclopropyl	SO2	CH	C ₂₅ H ₂₈ N ₄ O ₃ S
312165	3-F-4-[NH2C(=NH)]-PhCH2NHCO	SO2	CH	C ₂₃ H ₂₄ FN ₄ O ₄ S
312166	5-[NH2C(=NOH)]-2-thienyl-CH2NHCO	CH2	N	C ₂₁ H ₂₄ N ₆ O ₃ S

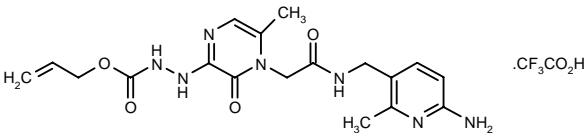
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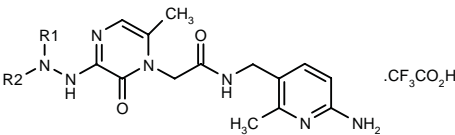
312167

3-[4-[N-(6-Amino-2-methylpyridin-3-ylmethyl)-carbamoylmethyl]-5-methyl-3-oxo-3,4-dihydropyrazin-2-yl]carbamic acid allyl ester trifluoroacetate



C18 H23 N7 O4 . C2 H F3 O2; Mol wt: 515.4466

ACTION – Anticoagulant, a thrombin inhibitor with high specificity for α-thrombin compared to other serine proteases, giving an IC₅₀ of 100 nM or less when tested for α-thrombin inhibition versus 100 μM or more in trypsin and factor Xa assays. Other exemplified compounds from this series of substituted hydrazinyl heteroaromatic compounds are:



Compound	R1	R2	Formula
312168	4-Cl-PhSO2	H	C ₂₀ H ₂₂ ClN ₇ O ₄ S.C ₂ HF ₃ O ₂
312169	ethynyl-CH2OCO	H	C ₁₈ H ₂₁ N ₇ O ₄ .C ₂ HF ₃ O ₂
312171	4-Cl-PhCH2NHCO	H	C ₂₂ H ₂₅ ClN ₈ O ₃ .C ₂ HF ₃ O ₂
312172	2-MeO-PhCH2NHCO	H	C ₂₃ H ₂₆ N ₈ O ₄ .C ₂ HF ₃ O ₂
312173	1,3-benzodioxol-5-yl- -CH2NHCO	H	C ₂₃ H ₂₆ N ₈ O ₅ .C ₂ HF ₃ O ₂
312174	2-F-PhSO2	H	C ₂₀ H ₂₂ FN ₇ O ₄ S.C ₂ HF ₃ O ₂
312175	Et	ethynyl- -CH2OCO	C ₂₀ H ₂₅ N ₇ O ₄ .C ₂ HF ₃ O ₂

SOURCE – Corvas.

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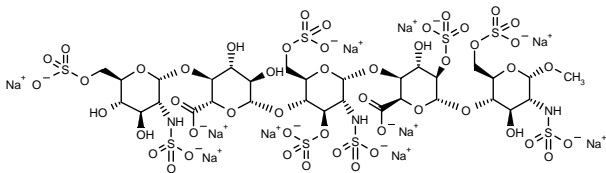
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FONDAPARINUX SODIUM
Prop INN

208310

O-[2-Deoxy-6-O-sulfo-2-(sulfoamino)-α-D-glucopyranosyl]-(1→4)-O-(β-D-glucopyranurosonyl)-(1→4)-O-[2-deoxy-3,6-di-O-sulfo-2-(sulfoamino)-α-D-glucopyranosyl]-(1→4)-O-(2-O-sulfo-α-L-idopyranurosonyl)-(1→4)-O-[2-deoxy-1-O-methyl-6-O-sulfo-2-(sulfoamino)-α-D-glucopyranoside] decasodium salt

Fondaparin sodium (former INN)
Org-31540
SR-90107A⁺



C31 H43 N3 Na10 O49 S8; Mol wt: 1728.0810

ACTION – Anticoagulant, a selective inhibitor of factor Xa.

INDICATION – Prophylaxis of deep vein thrombosis.

PRESENTATION – Single-dose, prefilled syringe containing 2.5 mg fondaparinux sodium in 0.5 ml.

PROPRIETARY NAME – Arixtra (US).

SOURCES – Organon; Sanofi-Synthélabo.

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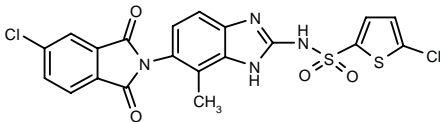
MONOGRAPH – Reverter, J.C. *Fondaparinux sodium.* Drugs Fut 2002, 27(2): 122.

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ANTIPLATELET THERAPY

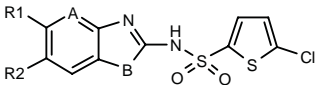
312837

5-Chloro-*N*-[6-(5-chloro-1,3-dioxo-2,3-dihydro-1*H*-indol-2-yl)-7-methyl-1*H*-benzimidazol-2-yl]thiophene-2-sulfonamide

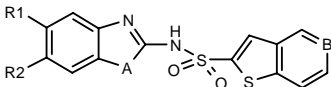


C20 H12 Cl2 N4 O4 S2; Mol wt: 507.3768

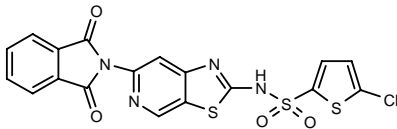
ACTION – Platelet ADP receptor inhibitor for the treatment and prevention of thrombosis, as well as other cardiovascular diseases such as acute myocardial infarction, angina pectoris, transient ischemic attacks, stroke, peripheral vascular disease, preeclampsia and eclampsia, deep vein thrombosis, embolism, disseminated intra-vascular coagulation, thrombocytopenic purpura and restenosis following invasive procedures resulting from angioplasty. Other specifically claimed heterocyclic sulfonamides include the following:



Compound	R1	R2	A	B	Formula
312838	H	1-oxo-2-isoindoliny	CH	NH	C ₁₉ H ₁₃ ClN ₄ O ₃ S ₂
312841	Br	1,3-dioxo-2-isoindoliny	CH	S	C ₁₉ H ₉ BrClN ₃ O ₃ S ₃
312844	H	NHCOPh	CH	NH	C ₁₈ H ₁₃ ClN ₄ O ₃ S ₂
312845	H	NHCOPh	CH	O	C ₁₈ H ₁₂ ClN ₃ O ₄ S ₂
312855	NHCOPh	H	N	O	C ₁₇ H ₁₁ ClN ₄ O ₄ S ₂
312857	2,4-dioxo-1,2,3,4-tetrahydro-3-quinazolinyl	H	CH	S	C ₁₉ H ₁₁ ClN ₄ O ₄ S ₃



Compound	R1	R2	A	B	Formula
312847	3-MeO-PhCONH	Br	S	N	C ₂₂ H ₁₅ BrN ₄ O ₄ S ₃
312849	1,3-benzodioxol-5-yl-CONH	H	O	C(Cl)	C ₂₃ H ₁₄ ClN ₃ O ₆ S ₂



312852: C18 H9 Cl N4 O4 S3

SOURCE – Millennium.

REFERENCES

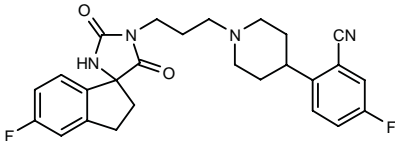
1. Scarborough, R.M. and Marlowe, C.K. (COR Therapeutics, Inc.) *Heterobicyclic sulfonamides and their use as platelet ADP receptor inhibitors.* WO 0185722.

RENAL-UROLOGIC DRUGS

BENIGN PROSTATIC HYPERPLASIA THERAPY

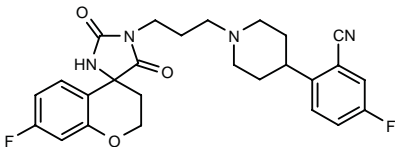
312409

(+)-5-Fluoro-2-[1-[3-[5'-fluoro-2,5-dioxo-2',3'-dihydro-1'*H*-spiro[imidazolidine-4,1'-inden]-1-yl]propyl]piperidin-4-yl]benzonitrile



C26 H26 F2 N4 O2; Mol wt: 464.5134

ACTION – An α_{1A} -adrenoceptor antagonist, expected to be useful for the treatment of benign prostatic hyperplasia. Another specifically claimed spirohydantoin derivative is:



312410: C26 H26 F2 N4 O3

SOURCE – Merck & Co.

REFERENCES

1. Hoffman, J.M. (Merck & Co., Inc.) *Spirohydantoin cpds. and uses thereof.* US 6316437.

37. *FDA issues approvable letter for Arixtra.* DailyDrugNews.com (Daily Essentials) 2001, Aug 22.

38. *Pentasaccharide registration submission and other important events at Sanofi-Synthelabo.* DailyDrugNews.com (Daily Essentials) 2001, Feb 21.

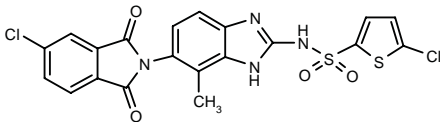
MONOGRAPH – Reverter, J.C. *Fondaparinux sodium.* Drugs Fut 2002, 27(2): 122.

*Drug Data Rep 1995, 017(11): 1004.

ANTIPLATELET THERAPY

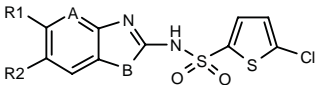
312837

5-Chloro-*N*-[6-(5-chloro-1,3-dioxo-2,3-dihydro-1*H*-indol-2-yl)-7-methyl-1*H*-benzimidazol-2-yl]thiophene-2-sulfonamide

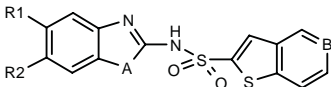


C20 H12 Cl2 N4 O4 S2; Mol wt: 507.3768

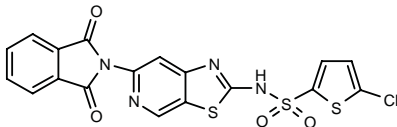
ACTION – Platelet ADP receptor inhibitor for the treatment and prevention of thrombosis, as well as other cardiovascular diseases such as acute myocardial infarction, angina pectoris, transient ischemic attacks, stroke, peripheral vascular disease, preeclampsia and eclampsia, deep vein thrombosis, embolism, disseminated intra-vascular coagulation, thrombocytopenic purpura and restenosis following invasive procedures resulting from angioplasty. Other specifically claimed heterocyclic sulfonamides include the following:



Compound	R1	R2	A	B	Formula
312838	H	1-oxo-2-isoindoliny	CH	NH	C ₁₉ H ₁₃ ClN ₄ O ₃ S ₂
312841	Br	1,3-dioxo-2-isoindoliny	CH	S	C ₁₉ H ₉ BrClN ₃ O ₃ S ₃
312844	H	NHCOPh	CH	NH	C ₁₈ H ₁₃ ClN ₄ O ₃ S ₂
312845	H	NHCOPh	CH	O	C ₁₈ H ₁₂ ClN ₃ O ₄ S ₂
312855	NHCOPh	H	N	O	C ₁₇ H ₁₁ ClN ₄ O ₄ S ₂
312857	2,4-dioxo-1,2,3,4-tetrahydro-3-quinazolinyl	H	CH	S	C ₁₉ H ₁₁ ClN ₄ O ₄ S ₃



Compound	R1	R2	A	B	Formula
312847	3-MeO-PhCONH	Br	S	N	C ₂₂ H ₁₅ BrN ₄ O ₄ S ₃
312849	1,3-benzodioxol-5-yl-CONH	H	O	C(Cl)	C ₂₃ H ₁₄ ClN ₃ O ₆ S ₂



312852: C18 H9 Cl N4 O4 S3

SOURCE – Millennium.

REFERENCES

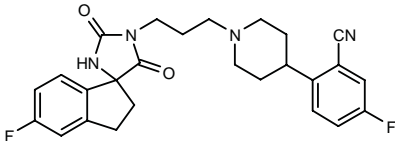
1. Scarborough, R.M. and Marlowe, C.K. (COR Therapeutics, Inc.) *Heterobicyclic sulfonamides and their use as platelet ADP receptor inhibitors.* WO 0185722.

RENAL-UROLOGIC DRUGS

BENIGN PROSTATIC HYPERPLASIA THERAPY

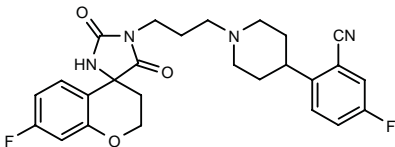
312409

(+)-5-Fluoro-2-[1-[3-[5'-fluoro-2,5-dioxo-2',3'-dihydro-1'*H*-spiro[imidazolidine-4,1'-inden]-1-yl]propyl]piperidin-4-yl]benzonitrile



C26 H26 F2 N4 O2; Mol wt: 464.5134

ACTION – An α_{1A} -adrenoceptor antagonist, expected to be useful for the treatment of benign prostatic hyperplasia. Another specifically claimed spirohydantoin derivative is:



312410: C26 H26 F2 N4 O3

SOURCE – Merck & Co.

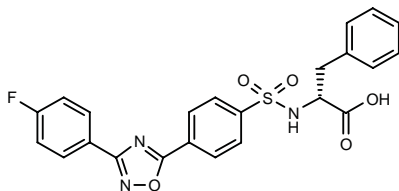
REFERENCES

1. Hoffman, J.M. (Merck & Co., Inc.) *Spirohydantoin cpds. and uses thereof.* US 6316437.

TREATMENT OF RENAL DISEASES

312991

N-[4-[3-(4-Fluorophenyl)-1,2,4-oxadiazol-5-yl]phenyl-sulfonyl]-D-phenylalanine



C23 H18 F N3 O5 S; Mol wt: 467.4752

ACTION – A representative compound within a series of oxadiazoles that inhibits matrix metalloproteinase MMP-2 (gelatinase A; IC_{50} = 0.051 μ M), as well as MMP-8 (neutrophil collagenase; IC_{50} = 0.52 μ M) and MMP-9 (gelatinase B; IC_{50} = 0.82 μ M). Potentially useful for the treatment of glomerular disorders, as demonstrated by inhibition of the elevation in BUN and urinary protein in a rat model.

SOURCE – Shionogi.

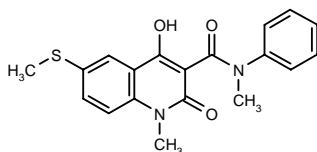
REFERENCES

- Shinosaki, T. et al. (Shionogi & Co. Ltd.) *Oxadiazole derivs. having therapeutic or preventive efficacies against glomerular disorders*. WO 0183464.

FR-137316

314279

4-Hydroxy-*N*,1-dimethyl-6-(methylsulfonyl)-2-oxo-*N*-phenyl-1,2-dihydroquinoline-3-carboxamide



C19 H18 N2 O3 S; Mol wt: 354.4282

ACTION – Antinephritic agent, a linomide derivative with high efficacy in chronic graft-versus-host disease, a murine model of human lupus nephritis, where it significantly inhibited proteinuria and DNA antibody formation (100 and 88% inhibition, respectively) at 10 mg/kg p.o., being about equipotent to prednisolone and much more active than linomide. Moreover, while prednisolone was toxic at a dose of 10 mg/kg, the compound was well tolerated up to 100 mg/kg. In spontaneous autoimmune disease MRL/1 mice, compound (1-10 mg/kg p.o.) was at least 100-fold more potent than the parent compound in suppressing proteinuria, glomerulonephritis and DNA autoantibody production.

SOURCE – Fujisawa.

REFERENCES

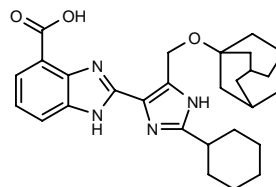
- Matsuo, M. et al. (Fujisawa Pharmaceutical Co., Ltd.) *Quinoline derivs*. EP 0639182, JP 1994506925, WO 9218483.
- Tsuji, K. et al. *Synthesis and antinephritic activities of quinoline-3-carboxamides and related compounds*. Bioorg Med Chem Lett 2002, 12(1): 85.

GASTROINTESTINAL DRUGS

ANTIULCER DRUGS

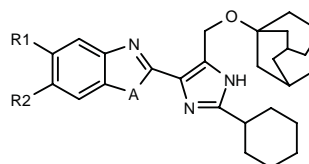
313118

2-[5-(Adamant-1-yloxymethyl)-2-cyclohexyl-1*H*-imidazol-4-yl]-1*H*-benzimidazole-4-carboxylic acid



C28 H34 N4 O3; Mol wt: 474.6016

ACTION – Gastrin and cholecystokinin (CCK) receptor ligand for use in the treatment of gastrointestinal disorders. This compound inhibited pentagastrin-induced acid secretion in immature rat stomach with a pK_B of 6.43, thus demonstrating gastrin (CCK_2)-antagonist activity. It is also reported to prevent hyperplasia when used in combination with proton pump inhibitors. Other exemplified compounds are:



Compound	R1	R2	A	Formula
313119	CO2H	H	O	C ₂₈ H ₃₃ N ₃ O ₄
313120	H	CO2H	O	C ₂₈ H ₃₃ N ₃ O ₄
313121	CO2H	H	NH	C ₂₈ H ₃₄ N ₄ O ₃
313122	CH2CO2H	H	O	C ₂₉ H ₃₅ N ₃ O ₄

SOURCE – James Black Foundation.

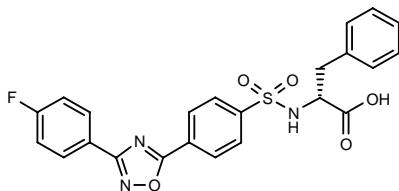
REFERENCES

- Kalindjian, S.B. et al. (James Black Foundation Ltd.) *Gastrin and cholecystokinin receptor ligands (III)*. WO 0185724.

TREATMENT OF RENAL DISEASES

312991

N-[4-[3-(4-Fluorophenyl)-1,2,4-oxadiazol-5-yl]phenyl-sulfonyl]-D-phenylalanine



C23 H18 F N3 O5 S; Mol wt: 467.4752

ACTION – A representative compound within a series of oxadiazoles that inhibits matrix metalloproteinase MMP-2 (gelatinase A; IC_{50} = 0.051 μ M), as well as MMP-8 (neutrophil collagenase; IC_{50} = 0.52 μ M) and MMP-9 (gelatinase B; IC_{50} = 0.82 μ M). Potentially useful for the treatment of glomerular disorders, as demonstrated by inhibition of the elevation in BUN and urinary protein in a rat model.

SOURCE – Shionogi.

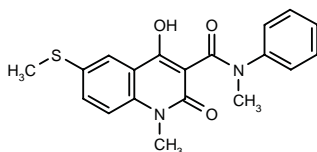
REFERENCES

- Shinosaki, T. et al. (Shionogi & Co. Ltd.) *Oxadiazole derivs. having therapeutic or preventive efficacies against glomerular disorders*. WO 0183464.

FR-137316

314279

4-Hydroxy-*N*,1-dimethyl-6-(methylsulfonyl)-2-oxo-*N*-phenyl-1,2-dihydroquinoline-3-carboxamide



C19 H18 N2 O3 S; Mol wt: 354.4282

ACTION – Antinephritic agent, a linomide derivative with high efficacy in chronic graft-versus-host disease, a murine model of human lupus nephritis, where it significantly inhibited proteinuria and DNA antibody formation (100 and 88% inhibition, respectively) at 10 mg/kg p.o., being about equipotent to prednisolone and much more active than linomide. Moreover, while prednisolone was toxic at a dose of 10 mg/kg, the compound was well tolerated up to 100 mg/kg. In spontaneous autoimmune disease MRL/1 mice, compound (1-10 mg/kg p.o.) was at least 100-fold more potent than the parent compound in suppressing proteinuria, glomerulonephritis and DNA autoantibody production.

SOURCE – Fujisawa.

REFERENCES

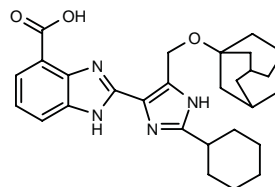
- Matsuo, M. et al. (Fujisawa Pharmaceutical Co., Ltd.) *Quinoline derivs*. EP 0639182, JP 1994506925, WO 9218483.
- Tsuji, K. et al. *Synthesis and antinephritic activities of quinoline-3-carboxamides and related compounds*. Bioorg Med Chem Lett 2002, 12(1): 85.

GASTROINTESTINAL DRUGS

ANTIULCER DRUGS

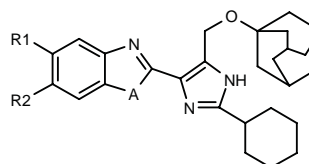
313118

2-[5-(Adamant-1-yloxymethyl)-2-cyclohexyl-1*H*-imidazol-4-yl]-1*H*-benzimidazole-4-carboxylic acid



C28 H34 N4 O3; Mol wt: 474.6016

ACTION – Gastrin and cholecystokinin (CCK) receptor ligand for use in the treatment of gastrointestinal disorders. This compound inhibited pentagastrin-induced acid secretion in immature rat stomach with a pK_B of 6.43, thus demonstrating gastrin (CCK_2)-antagonist activity. It is also reported to prevent hyperplasia when used in combination with proton pump inhibitors. Other exemplified compounds are:



Compound	R1	R2	A	Formula
313119	CO2H	H	O	C ₂₈ H ₃₃ N ₃ O ₄
313120	H	CO2H	O	C ₂₈ H ₃₃ N ₃ O ₄
313121	CO2H	H	NH	C ₂₈ H ₃₄ N ₄ O ₃
313122	CH2CO2H	H	O	C ₂₉ H ₃₅ N ₃ O ₄

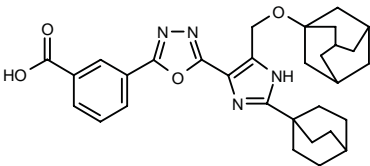
SOURCE – James Black Foundation.

REFERENCES

- Kalindjian, S.B. et al. (James Black Foundation Ltd.) *Gastrin and cholecystokinin receptor ligands (III)*. WO 0185724.

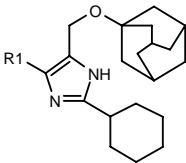
313127

3-[5-[5-(Adamant-1-yloxymethyl)-2-(bicyclo[2.2.2]oct-1-yl)-1*H*-imidazol-4-yl]-1,3,4-oxadiazol-2-yl]benzoic acid



C31 H36 N4 O4; Mol wt: 528.6494

ACTION – Gastrin and cholecystokinin (CCK) receptor ligand for use in the treatment of gastrointestinal disorders. This compound inhibited pentagastrin-induced acid secretion in immature rat stomach with a pK_B of 8.72, thus demonstrating gastrin (CCK₂)-antagonist activity. It is also reported to prevent hyperplasia when used in combination with proton pump inhibitors. Other exemplified compounds are:



Compound	R1	Formula
313128	3-(3-CO2H-Ph)-1,2,4-oxadiazol-5-yl	C ₂₉ H ₃₄ N ₄ O ₄
313129	4-(3-CO2H-Ph)-2-thiazolyl	C ₃₀ H ₃₅ N ₃ O ₃ S
313130	5-(3-CO2H-Ph)-1,3,4-thiadiazol-2-yl	C ₂₈ H ₃₄ N ₄ O ₃ S
313131	5-(3-CO2H-Ph)-1,3,4-oxadiazol-2-yl	C ₂₉ H ₃₄ N ₄ O ₄
313132	5-(3-CO2H-Ph)-1,2,4-oxadiazol-3-yl	C ₂₉ H ₃₄ N ₄ O ₄

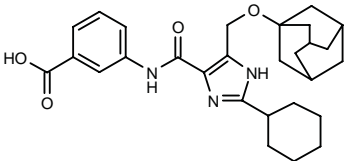
SOURCE – James Black Foundation.

REFERENCES

1. Kalindjian, S.B. et al. (James Black Foundation Ltd.) *Gastrin and cholecystokinin receptor ligands (II)*. WO 0185723.

313133

3-[5-(Adamant-1-yloxymethyl)-2-cyclohexyl-1*H*-imidazol-4-ylcarboxamido]benzoic acid



C28 H35 N3 O4; Mol wt: 477.6015

ACTION – Gastrin and cholecystokinin (CCK) receptor ligand for use in the treatment of gastrointestinal disorders. This compound inhibited pentagastrin-induced acid secretion in immature rat stomach, thus demonstrating gastrin (CCK₂)-antagonist activity. It is also reported to prevent hyperplasia when used in combination with proton pump inhibitors.

SOURCES – James Black Foundation; Janssen.

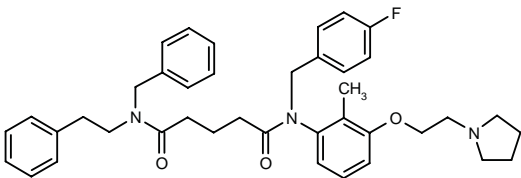
REFERENCES

1. Kalindjian, S.B. et al. (Janssen Pharmaceutica NV;James Black Foundation Ltd.) *Pharmaceutical compsns. comprising proton pump inhibitors and gastrin/cholecystokinin receptor ligands*. WO 0185167.

AGENTS FOR IRRITABLE BOWEL SYNDROME

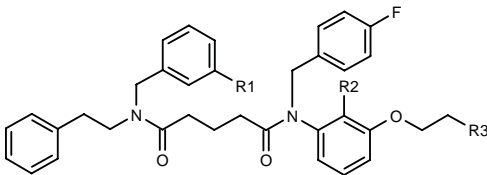
312865

*N*¹-Benzyl-*N*⁵-(4-fluorobenzyl)-*N*⁵-[2-methyl-3-[2-(1-pyrrolidinyl)ethoxy]phenyl]-*N*¹-(2-phenylethyl)pentane-diamide

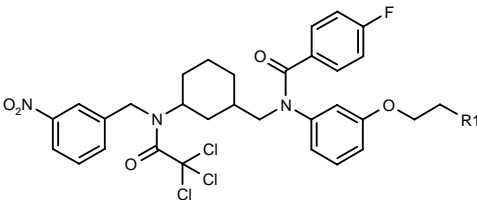


C40 H46 F N3 O3; Mol wt: 635.8194

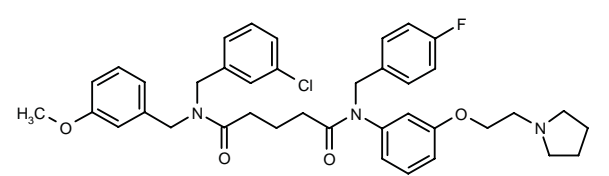
ACTION – Motilin receptor antagonist (IC₅₀ = 0.006 μM) proven to inhibit motilin binding by 100% in rabbit colon. Potentially useful for the treatment of gastrointestinal reflux disorders, eating disorders and irritable bowel syndrome. Other exemplified substituted diamine derivatives include the following:



Compound	R1	R2	R3	Formula
312871	H	H	N(Et)2	C ₃₉ H ₄₆ FN ₃ O ₃
312872	H	H	N(Me)2	C ₃₇ H ₄₂ FN ₃ O ₃
312874	H	H	CH2N(Me)2	C ₃₈ H ₄₄ FN ₃ O ₃
312875	H	H	1-Pip-CH2	C ₄₁ H ₄₈ FN ₃ O ₃
312878	CO2H	Me	1-pyrrolidinyl	C ₄₁ H ₄₆ FN ₃ O ₅



Compound	R1	Isomer	Formula
312867	4-morpholinyl		C ₃₅ H ₃₆ Cl ₃ FN ₄ O ₆
312877	1-pyrrolidinyl	cis	C ₃₅ H ₃₆ Cl ₃ FN ₄ O ₅



312876: C39 H43 Cl F N3 O4

SOURCE – Ortho-McNeil.

REFERENCES

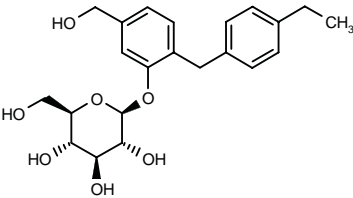
1. Johnson, S.G. and Rivero, R.A. (Ortho-McNeil Pharmaceuticals, Inc.) *Novel subst. diamine derivs. useful as motilin antagonists.* WO 0185694.

ENDOCRINE DRUGS

ANTIDIABETIC DRUGS

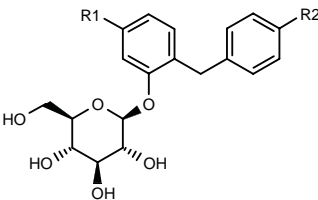
310275

1-*O*-[2-(4-Ethylbenzyl)-5-(hydroxymethyl)phenyl]-β-D-glucopyranoside



C22 H28 O7; Mol wt: 404.4562

ACTION – Agent with the ability to inhibit the human sodium-dependent glucose transporter type 2 (SGLT2), and thus potentially useful for the treatment of diabetes and obesity. In *in vitro* assays, compound gave an IC₅₀ of 8.1 nM against SGLT2 expressed in COS-7 cells. It promoted urinary glucose excretion in rats when administered at a dose of 1 mg/kg i.v. Other exemplified aryl-substituted glucopyranosides are:



Compound	R1	R2	Formula
310276	H	OMe	C ₂₀ H ₂₄ O ₇
310277	CH2OH	OPr	C ₂₃ H ₃₀ O ₈
310279	H	CH2CH2OH	C ₂₁ H ₂₆ O ₇

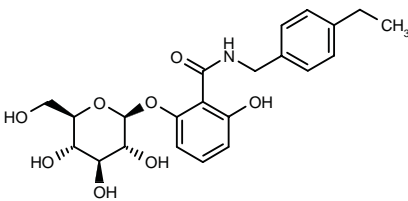
SOURCE – Kissei.

REFERENCES

1. Fujikura, H. et al. (Kissei Pharmaceutical Co., Ltd.) *Glucopyranosyloxy benzylbenzene derivs., medicinal compsns. containing the same and intermediates for the preparation of the derivs..* WO 0168660.

311843

N-(4-Ethylbenzyl)-2-(β-D-glucopyranosyloxy)-6-hydroxybenzamide



C22 H27 N O8; Mol wt: 433.4543

ACTION – A representative compounds from a series of *O*-glucosylated benzamides that inhibits the sodium-dependent glucose transporter SGLT2. Potentially useful for the treatment of type 2 diabetes, as well as for diabetic complications, wound healing, insulin resistance, hyperinsulinemia, hyperglycemia, hyperlipidemia, syndrome X, obesity, atherosclerosis and hypertension.

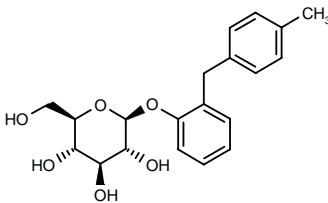
SOURCE – Bristol-Myers Squibb.

REFERENCES

1. Washburn, W.N. (Bristol-Myers Squibb Co.) *O-Glucosylated benzamide SGLT2 inhibitors and method.* WO 0174835.

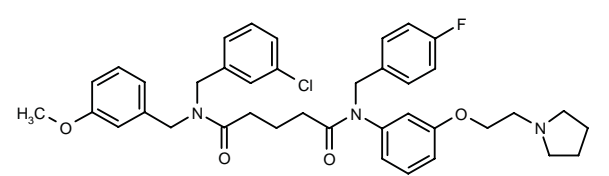
311845

1-*O*-[2-(4-Methylbenzyl)phenyl]-β-D-glucopyranoside



C20 H24 O6; Mol wt: 360.4036

ACTION – An inhibitor of the sodium-dependent glucose transporter SGLT2, expected to be useful for the treatment of type 2 diabetes, as well as diabetic complications, wound healing, insulin resistance, hyperinsulinemia, hyperglycemia, hyperlipidemia, syndrome X, obesity, atherosclerosis and hypertension. Other exemplified *O*-aryl glucosides include the following:



312876: C39 H43 Cl F N3 O4

SOURCE – Ortho-McNeil.

REFERENCES

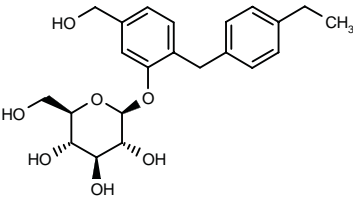
1. Johnson, S.G. and Rivero, R.A. (Ortho-McNeil Pharmaceuticals, Inc.) *Novel subst. diamine derivs. useful as motilin antagonists.* WO 0185694.

ENDOCRINE DRUGS

ANTIDIABETIC DRUGS

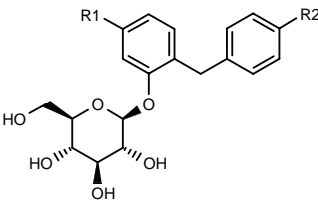
310275

1-*O*-[2-(4-Ethylbenzyl)-5-(hydroxymethyl)phenyl]-β-D-glucopyranoside



C22 H28 O7; Mol wt: 404.4562

ACTION – Agent with the ability to inhibit the human sodium-dependent glucose transporter type 2 (SGLT2), and thus potentially useful for the treatment of diabetes and obesity. In *in vitro* assays, compound gave an IC₅₀ of 8.1 nM against SGLT2 expressed in COS-7 cells. It promoted urinary glucose excretion in rats when administered at a dose of 1 mg/kg i.v. Other exemplified aryl-substituted glucopyranosides are:



Compound	R1	R2	Formula
310276	H	OMe	C ₂₀ H ₂₄ O ₇
310277	CH2OH	OPr	C ₂₃ H ₃₀ O ₈
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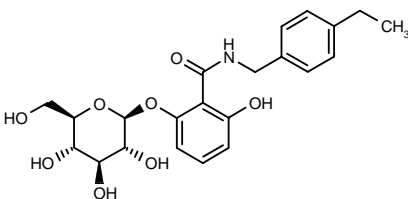
SOURCE – Kissei.

REFERENCES

1. Fujikura, H. et al. (Kissei Pharmaceutical Co., Ltd.) *Glucopyranosyloxy benzylbenzene derivs., medicinal compsns. containing the same and intermediates for the preparation of the derivs..* WO 0168660.

311843

N-(4-Ethylbenzyl)-2-(β-D-glucopyranosyloxy)-6-hydroxybenzamide



C22 H27 N O8; Mol wt: 433.4543

ACTION – A representative compounds from a series of *O*-glucosylated benzamides that inhibits the sodium-dependent glucose transporter SGLT2. Potentially useful for the treatment of type 2 diabetes, as well as for diabetic complications, wound healing, insulin resistance, hyperinsulinemia, hyperglycemia, hyperlipidemia, syndrome X, obesity, atherosclerosis and hypertension.

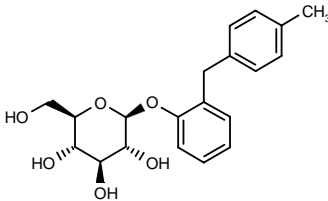
SOURCE – Bristol-Myers Squibb.

REFERENCES

1. Washburn, W.N. (Bristol-Myers Squibb Co.) *O-Glucosylated benzamide SGLT2 inhibitors and method.* WO 0174835.

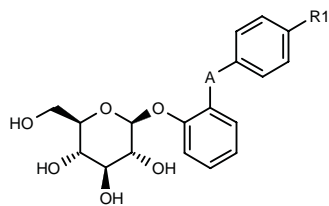
311845

1-*O*-[2-(4-Methylbenzyl)phenyl]-β-D-glucopyranoside



C20 H24 O6; Mol wt: 360.4036

ACTION – An inhibitor of the sodium-dependent glucose transporter SGLT2, expected to be useful for the treatment of type 2 diabetes, as well as diabetic complications, wound healing, insulin resistance, hyperinsulinemia, hyperglycemia, hyperlipidemia, syndrome X, obesity, atherosclerosis and hypertension. Other exemplified *O*-aryl glucosides include the following:



Compound	R1	A	Formula
311846	Et	CH2	C ₂₁ H ₂₆ O ₆
311847	Me	O	C ₁₉ H ₂₂ O ₇
311848	H	NH	C ₁₈ H ₂₁ NO ₆
311850	Me	S	C ₁₉ H ₂₂ O ₆ S

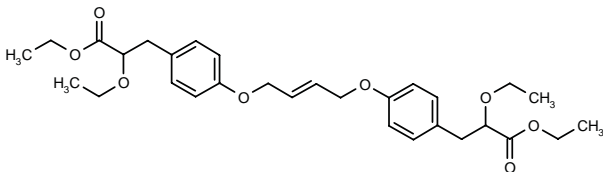
SOURCE – Bristol-Myers Squibb.

REFERENCES

1. Washburn, W.N. et al. (Bristol-Myers Squibb Co.) *O-Aryl glucoside SGLT2 inhibitors and method.* WO 0174834.

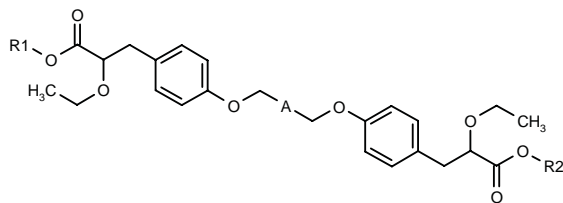
312257

3,3'-(2-Butene-1,4-diyl)bis(oxy)bis(4,1-phenylene)bis(2-ethoxypropionic acid ethyl ester)



C30 H40 O8; Mol wt: 528.6380

ACTION – Dual agonist of peroxisome proliferator-activated receptors PPARα and PPARγ, potentially useful for the treatment of diabetes and obesity. Other specifically claimed dicarboxylic acid compounds are:



Compound	R1	R2	A	Formula
312259	H	H	-CH=CH-	C ₂₆ H ₃₂ O ₈
312260	Et	Et	-1,4-Ph-	C ₃₄ H ₄₂ O ₈
312261	Et	Et	-ethynylene-	C ₃₀ H ₃₈ O ₈
312262	H	Et	-1,4-Ph-	C ₃₂ H ₃₈ O ₈
312264	H	Et	-ethynylene-	C ₂₈ H ₃₄ O ₈

SOURCE – Novo Nordisk.

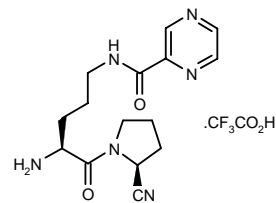
REFERENCES

1. Sauerberg, P. et al. (Novo Nordisk A/S) *New cpds., their preparation and use.* WO 0179150.

312349

N-[4 (S)-Amino-5-[2 (S)-cyanopyrrolidin-1-yl]-5-oxopentyl]pyrazine-2-carboxamide trifluoroacetate

1-[N⁵-(Pyrazin-2-ylcarbonyl)-L-ornithyl]pyrrolidine-2 (S)-carbonitrile trifluoroacetate



C15 H20 N6 O2 . C2 H F3 O2; Mol wt: 430.3849

ACTION – A dipeptidyl-peptidase IV (DPP-IV) inhibitor, potentially useful for the treatment of type 2 diabetes, impaired glucose tolerance, growth hormone deficiency and polycystic ovary syndrome, as well as autoimmune and inflammatory diseases.

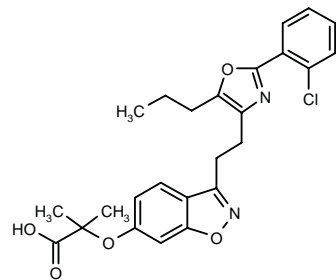
SOURCE – Ferring.

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1. Evans, D.M. and Pitt, G.R.W. (Ferring BV Group Holding) *Inhibitors of dipeptidyl peptidase IV.* WO 0181304.

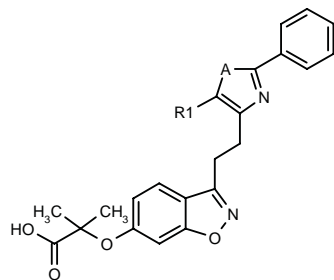
312796

2-[3-[2-[2-(2-Chlorophenyl)-5-propyloxazol-4-yl]ethyl]-1,2-benzisoxazol-6-yloxy]-2-methylpropionic acid



C25 H25 Cl N2 O5; Mol wt: 468.9345

ACTION – Agent with the ability to activate peroxisome proliferator-activated PPARδ receptors, potentially useful as a blood glucose- and lipid-lowering agent. It increased the activity of PPARδ receptors in monkey renal fibroblast CV-1 cells by 73% at 10 μM. Other exemplified benzisoxazoles are:



Compound	R1	A	Formula
312797	Me	O	C ₂₃ H ₂₂ N ₂ O ₅
312798	Et	O	C ₂₄ H ₂₄ N ₂ O ₅
312799	Pr	O	C ₂₅ H ₂₆ N ₂ O ₅
312800	Bu	O	C ₂₆ H ₂₈ N ₂ O ₅
312801	Ph	O	C ₂₈ H ₂₄ N ₂ O ₅
312802	Me	S	C ₂₃ H ₂₂ N ₂ O ₄ S

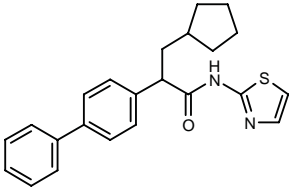
SOURCE – Nippon Chemiphar.

REFERENCES

1. Sakuma, S. et al. (Nippon Chemiphar Co., Ltd.) *Activators for peroxisome proliferator activated receptor δ (PPAR δ)*. JP 2001354671, WO 0179197.

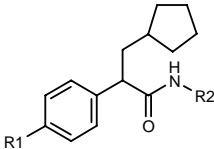
312907

2-(4-Biphenyl)-3-cyclopentyl-N-(2-thiazolyl)propionamide



C23 H24 N2 O S; Mol wt: 376.5216

ACTION – Glucokinase activator, potentially useful for the treatment of type 2 diabetes mellitus. Other specifically claimed substituted phenylacetamides are:



Compound	R1	R2	Formula
312908	Ph	4-(CO2Me)-2-thiazolyl	C ₂₅ H ₂₆ N ₂ O ₃ S
312909	1-Naph	4-(CH2OH)-2-thiazolyl	C ₂₆ H ₂₈ N ₂ O ₂ S
312910	5-indolyl	2-thiazolyl	C ₂₅ H ₂₅ N ₃ OS
312911	OPh	4-(CO2HCH2)-2-thiazolyl	C ₂₅ H ₂₆ N ₂ O ₄ S
312912	3-Pyr	CONHMe	C ₂₁ H ₂₅ N ₃ O ₂

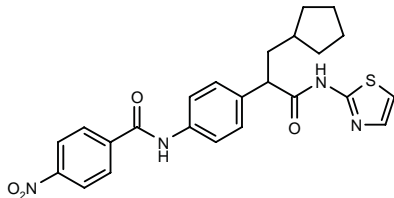
SOURCE – Roche.

REFERENCES

1. Corbett, W.L. et al. (F. Hoffmann-La Roche AG) *Substd. phenylacetamides and their use as glucokinase activators*. WO 0185706.

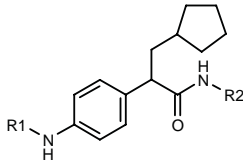
312913

N-[4-[2-Cyclopentyl-1-[N-(2-thiazolyl)carbamoyl]-ethyl]phenyl]-4-nitrobenzamide



C24 H24 N4 O4 S; Mol wt: 464.5436

ACTION – Glucokinase activator, potentially useful for the treatment of type 2 diabetes mellitus. Other specifically claimed substituted phenylacetamides are:



Compound	R1	R2	Formula
312914	4-Pyr-CO	2-thiazolyl	C ₂₃ H ₂₄ N ₄ O ₂ S
312915	3-Pyr-CO	2-Pyr	C ₂₅ H ₂₆ N ₄ O ₂
312916	COCH2CO2Me	2-thiazolyl	C ₂₁ H ₂₅ N ₃ O ₄ S
312917	4-NO2-PhSO2	2-thiazolyl	C ₂₃ H ₂₄ N ₄ O ₅ S ₂

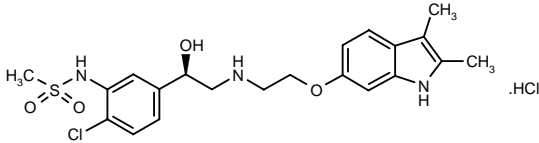
SOURCE – Roche.

REFERENCES

1. Bizzarro, F.T. et al. (F. Hoffmann-La Roche AG) *Para-amine substd. phenylamide glucokinase activators*. WO 0185707.

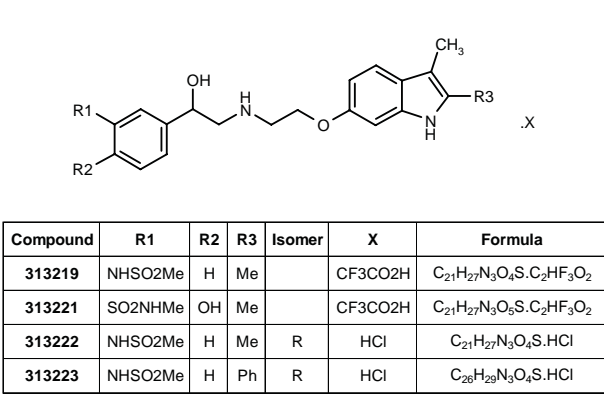
313218

N-[2-Chloro-5-[2-[2-(2,3-dimethyl-1H-indol-6-yloxy)-ethylamino]-1(R)-hydroxyethyl]phenyl]methanesulfonamide hydrochloride



C21 H26 Cl N3 O4 S . HCl; Mol wt: 488.4333

ACTION – Selective β₃-adrenoceptor agonist, as demonstrated in CHO cells expressing the human β₃-adrenoceptor (EC₅₀ = 4.5 nM). It exhibited hypoglycemic and lipolytic effects in glucose-loaded mice, as well as low toxicity, and is also reported to have little effect on the heart. Potentially useful for the treatment or prevention of diabetes, obesity, hyperlipidemia, etc. Other exemplified bicyclic compounds are:



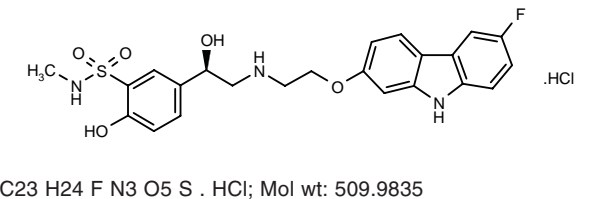
SOURCE – Asahi Kasei.

REFERENCES

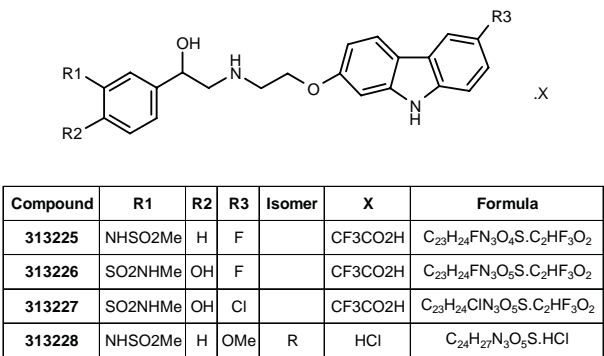
1. Ikuta, S. et al. (Asahi Kasei Corp.) *Novel bicyclic cpds.* WO 0183451.

313224

5-[2-[2-(6-Fluoro-9*H*-carbazol-2-yloxy)ethylamino]-1(*R*)-hydroxyethyl]-2-hydroxy-*N*-methylbenzenesulfonamide hydrochloride



ACTION – Selective β_3 -adrenoceptor agonist, as demonstrated in CHO cells expressing the human β_3 -adrenoceptor (EC₅₀ = 9.1 nM). It exhibited hypoglycemic and lipolytic effects in glucose-loaded mice, as well as low toxicity, and is also reported to have little effect on the heart. Potentially useful for the treatment or prevention of diabetes, obesity, hyperlipidemia, etc. Other exemplified tricyclic compounds are:



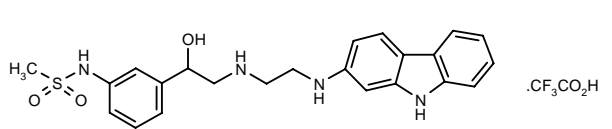
SOURCE – Asahi Kasei.

REFERENCES

1. Ikuta, S. et al. (Asahi Kasei Corp.) *Novel subst. tricyclic cpds.* WO 0183453.

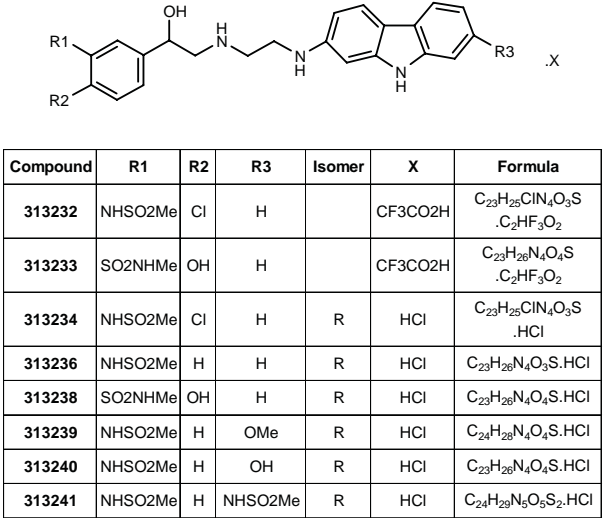
313230

N-[3-[2-[2-(9*H*-Carbazol-2-ylamino)ethylamino]-1-hydroxyethyl]phenyl]methanesulfonamide trifluoroacetate



C₂₃ H₂₆ N₄ O₃ S . C₂ H F₃ O₂; Mol wt: 552.5713

ACTION – Selective β_3 -adrenoceptor agonist, as demonstrated in CHO cells expressing the human β_3 -adrenoceptor (EC₅₀ = 2.0 nM). It exhibited hypoglycemic and lipolytic effects in glucose-loaded mice, as well as low toxicity, and is also reported to have little effect on the heart. Potentially useful for the treatment or prevention of diabetes, obesity, hyperlipidemia, etc. Other exemplified tricyclic compounds are:



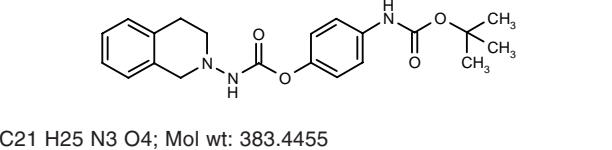
SOURCE – Asahi Kasei.

REFERENCES

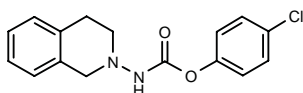
1. Ikuta, S. et al. (Asahi Kasei Corp.) *Novel tricyclic cpds.* WO 0183452.

313245

N-(1,2,3,4-Tetrahydroisoquinolin-2-yl)carbamic acid 4-(*tert*-butoxycarbonylamino)phenyl ester



ACTION – Agent with the ability to decrease plasma levels of free fatty acids through inhibition of hormone-sensitive lipase (HSL; $IC_{50} = 0.003 \mu M$), while being devoid of activity against lipoprotein lipase (LPL) and hepatic lipase (HL) (0 and 3% inhibition, respectively, at $50 \mu M$). Potentially useful for the treatment of type 2 diabetes, insulin resistance, impaired glucose tolerance, hyperglycemia, dyslipidemia and abnormalities of lipoprotein metabolism. Another exemplified carbamic acid analogue is:



313247: C16 H15 Cl N2 O2

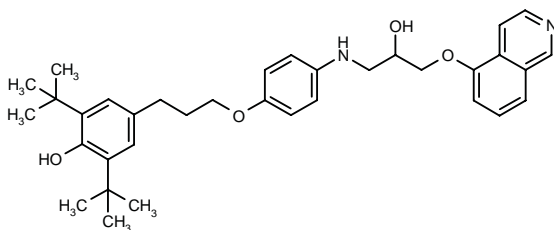
SOURCE – Novo Nordisk.

REFERENCES

1. Beltrandelrio, H. et al. (Novo Nordisk A/S) *Cpds. for treating disorders where a decreased level of plasma FFA is desired*. WO 0187843.

314245

2,6-Di-*tert*-butyl-4-[3-[4-[2-hydroxy-3-(isoquinolin-5-yloxy)propylamino]phenoxy]propyl]phenol



C35 H44 N2 O4; Mol wt: 556.7426

ACTION – Potential antidiabetic agent with β_3 -adrenoceptor-agonist activity (measured as cAMP stimulation in COS-7 cells transfected with β_3 -adrenoceptors) and antioxidant activity.

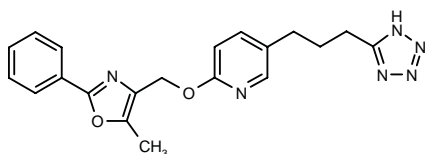
SOURCES – CNRS; Duke University, Durham, NC (US); Université Joseph Fourier, Grenoble (FR).

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1. Aubriot, S. et al. *New series of aryloxypropanolamines with both human β_3 -adrenoceptor agonistic activity and free radical scavenging properties*. Bioorg Med Chem Lett 2002, 12(2): 209.

314641

2-(5-Methyl-2-phenyloxazol-4-ylmethoxy)-5-[3-(1*H*-tetrazol-5-yl)propyl]pyridine



C20 H20 N6 O2; Mol wt: 376.4180

ACTION – Peroxisome proliferator-activated receptor PPAR γ agonist ($EC_{50} = 6.75 \text{ nM}$) with potent glucose- and lipid-lowering effects in KKA γ mice ($ED_{25} = 0.0839$ and 0.13 mg/kg/day in the diet, respectively), as well as in Wistar fatty rats ($ED_{25} = 0.0873$ and 0.0277 mg/kg/day in the diet, respectively). In the mouse model, compound was 72-fold more active than pioglitazone ($ED_{25} = 6.0 \text{ mg/kg day}$ in the diet), and in rats it was at least comparable to pioglitazone. Potentially useful for the treatment of type 2 diabetes.

SOURCE – Takeda.

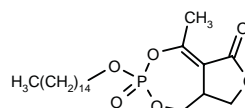
REFERENCES

1. Sohda, T. et al. (Takeda Chemical Industries, Ltd.) *Tetrazole derivs., their production and use*. CA 2125549, EP 0629624, JP 1995053555, US 5591862.
2. Momose, Y. et al. *Novel 5-substituted-1*H*-tetrazole derivatives as potent glucose and lipid lowering agents*. Chem Pharm Bull 2002, 50(1): 100.

CYCLIPOSTIN R

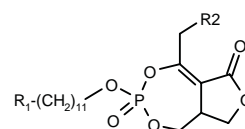
312654

5-Methyl-3-(pentadecyloxy)-1,6,8,8a-tetrahydrofuro-[3,4-*e*][1,3,2]dioxaphosphepin-6-one 3-oxide



C22 H39 O6 P; Mol wt: 430.5181

ACTION – A compound isolated from a culture of *Streptomyces* sp. HAG 004107 (DSM 13381) that acts as a lipase inhibitor ($IC_{50} = 10 \text{ nM}$ for inhibition of hormone-sensitive lipase [HSL]). Potentially useful for the treatment of type 2 diabetes mellitus. Other cyclipostins isolated from the same source are:



Compound	R1	R2	Formula
Cyclipostin A [312655]	CH(OH)Bu	H	C ₂₃ H ₄₁ O ₇ P
Cyclipostin N [312656]	Pr	H	C ₂₁ H ₃₇ O ₆ P
Cyclipostin P [312657]	C5H11	H	C ₂₃ H ₄₁ O ₆ P
Cyclipostin P2 [312660]	i-BuCH2	H	C ₂₃ H ₄₁ O ₆ P
Cyclipostin R2 [312661]	i-Bu	H	C ₂₂ H ₃₉ O ₆ P
Cyclipostin S [312663]	C5H11	Me	C ₂₄ H ₄₃ O ₆ P
Cyclipostin T [312664]	C5H11	Et	C ₂₅ H ₄₅ O ₆ P
Cyclipostin T2 [312665]	i-BuCH2	Et	C ₂₅ H ₄₅ O ₆ P

SOURCE – Aventis Pharma.

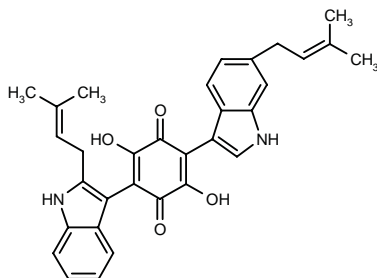
REFERENCES

1. Vertesy, L. et al. (Aventis Pharma Deutschland GmbH) *Cyclipostins, a method for their production and the use of the same*. DE 10021731, WO 0183497.

TAN-2547A

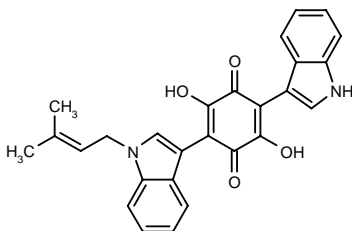
312928

2,5-Dihydroxy-3-[2-(3-methyl-2-butenyl)-1*H*-indol-3-yl]-6-[6-(3-methyl-2-butenyl)-1*H*-indol-3-yl]-1,4-benzoquinone



C32 H30 N2 O4; Mol wt: 506.5990

ACTION – Protein-tyrosine-phosphatase (PTP) inhibitor isolated from the fungus *Didymobotryum rigium* NF-12442. It inhibited human PTP1B activity with an IC₅₀ of 1.2 μM and demonstrated glucose uptake-promoting activity in *in vitro* studies. Compound is particularly indicated for the treatment of diabetes. Another compound from the same source is:



TAN-2547D [312929]: C27 H22 N2 O4

SOURCE – Tanabe Seiyaku.

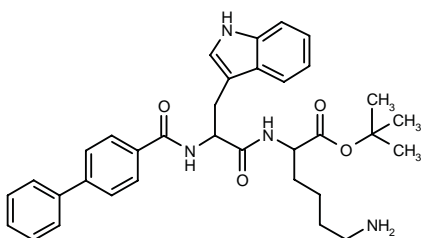
REFERENCES

1. Hayashi, K. et al. (Takeda Chemical Industries, Ltd.) *TAN-2547-related cpds., their preparation method and use.* JP 2001302629.

TREATMENT OF GROWTH HORMONE SECRETION DISORDERS

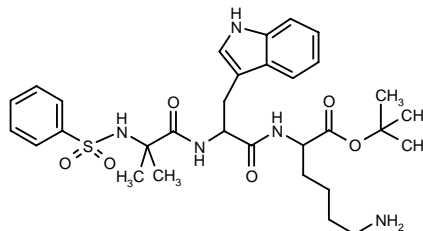
312056

N-(Biphenyl-4-ylcarbonyl)-DL-tryptophyl-DL-lysine *tert*-butyl ester



C34 H40 N4 O4; Mol wt: 568.7140

ACTION – A somatostatin sst₂ receptor antagonist reported to be useful for increasing growth hormone secretion from the pituitary. Potentially useful for the treatment of diseases characterized by reduced levels of growth hormone including frailty, hypoglycemia, wrinkled skin, slow skeletal growth, reduced immune function and reduced organ function. Another specifically claimed compound is:



312057: C31 H43 N5 O6 S

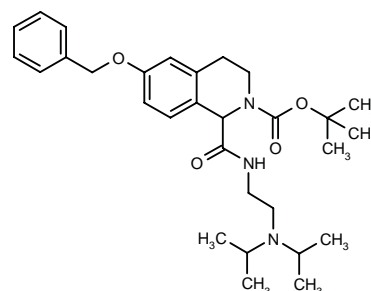
SOURCE – Pfizer.

REFERENCES

1. Cole, B.M. et al. (Pfizer Products Inc.) *Somatostatin antagonists and agonists that act at the sst subtype 2 receptor.* EP 1149842.

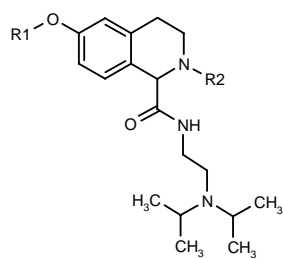
313134

6-(Benzyloxy)-1-[*N*-[2-(diisopropylamino)ethyl]-carbamoyl]-1,2,3,4-tetrahydroisoquinoline-2-carboxylic acid *tert*-butyl ester

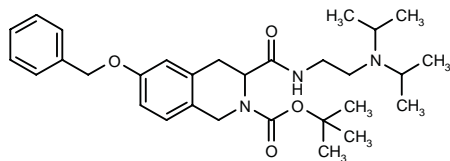


C30 H43 N3 O4; Mol wt: 509.6867

ACTION – Growth hormone secretagogue, potentially useful for the treatment of obesity and osteoporosis, as well as renal diseases, cachexia, anorexia, sleep disorders, depression, syndrome X, diabetes, congestive heart failure, cardiac myopathy, cardiac dysfunction, HIV wasting syndrome, muscular atrophy, lipodystrophy and wound healing. Other specifically claimed 1,2,3,4-tetrahydroisoquinoline analogues are:



Compound	R1	R2	Formula
313136	cyclohexyl-CH2	t-BuOCO	C ₃₀ H ₄₉ N ₃ O ₄
313137	Ph	t-BuOCO	C ₂₉ H ₄₁ N ₃ O ₄
313138	4-MeO-Ph	t-BuOCO	C ₃₀ H ₄₃ N ₃ O ₅
313139	Ph	CO ₂ C(Me)2CONHCH2CF ₃	C ₃₁ H ₄₁ F ₃ N ₄ O ₅
313140	Ph	CO ₂ (CH ₂) ₄ OH	C ₂₉ H ₄₁ N ₃ O ₅
313141	Ph	2-(MeSO ₂)-PhCO	C ₃₂ H ₃₉ N ₃ O ₅ S
313142	4-MeO-Ph	SO ₂ N(Me)2	C ₂₇ H ₄₀ N ₄ O ₅ S



313135: C30 H43 N3 O4

SOURCE – Bristol-Myers Squibb.

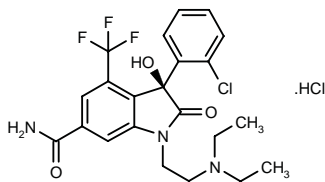
REFERENCES

1. Li, J.J. and Tino, J.A. (Bristol-Myers Squibb Co.) *Tetrahydroisoquinoline analogs useful as growth hormone secretagogues*. WO 0185695.

SM-130686*

286920

(+)-3(*S*)-(2-Chlorophenyl)-1-[2-(diethylamino)ethyl]-3-hydroxy-2-oxo-4-(trifluoromethyl)-2,3-dihydro-1*H*-indole-6-carboxamide hydrochloride



C22 H23 Cl F3 N3 O3 . HCl; Mol wt: 506.3496

ACTION – Potent, orally active growth hormone secretagogue (GHS; EC₅₀ = 3 nM in rat pituitary cells) with nanomolar affinity for the human GHS receptor (IC₅₀ = 1.2 nM) and no activity against a panel of other receptors and enzymes at up to 1 μM. In rats, compound increased body weight in a dose-dependent manner (3-30 mg/kg p.o.); at the dose of 10 mg/kg p.o. b.i.d. for 9 days, it significantly increased both body weight and lean body mass. Compound exhibited a favorable pharmacokinetic profile in rats, with 28% oral bioavailability. Potentially useful for the treatment of GH deficiency.

SOURCE – Sumitomo Pharmaceuticals.

REFERENCES

1. Tokunaga, T. et al. (Sumitomo Pharmaceuticals Co., Ltd.) *Oxindole derivs. as growth hormone releasers*. EP 1105376, WO 0010975.

2. Nagamine, J. et al. *Pharmacological effect of SM-130686, a novel GH secretagogue*. Folia Endocrinol Jpn 2000, 76(1): 172.

3. Nagamine, J. et al. *Pharmacological profile of a new orally active growth hormone secretagogue, SM-130686*. J Endocrinol 2001, 171(3): 481.

4. Nagata, R. et al. *Oxindole derivatives as orally active potent growth hormone secretagogues*. 220th ACS Natl Meet (Aug 20-24, Washington DC) 2000, Abst MEDI 309.

5. Tokunaga, T. et al. *Oxindole derivatives as orally active potent growth hormone secretagogues*. J Med Chem 2001, 44(26): 4641.

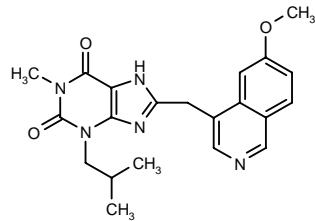
6. Tokunaga, T. et al. *Synthesis and biological evaluation of oxindole derivatives as novel growth hormone secretagogues*. 222nd ACS Natl Meet (Aug 26-30, Chicago) 2001, Abst MEDI 186.

*Identified compound **286920** Drug Data Rep 2000, 022(06): 0527.

TREATMENT OF MALE SEXUAL DYSFUNCTION

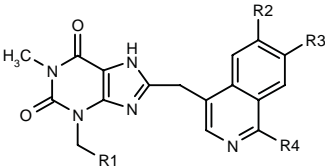
312068

3-Isobutyl-8-(6-methoxyisoquinolin-4-ylmethyl)-1-methylxanthine



C21 H23 N5 O3; Mol wt: 393.4447

ACTION – Phosphodiesterase type 5 (PDE5) inhibitor (IC₅₀ = 0.002 μM), potentially useful for the treatment of erectile dysfunction. Other exemplified xanthine derivatives are:



Compound	R1	R2	R3	R4	Formula
312069	i-Pr	OMe	OMe	Me	C ₂₃ H ₂₇ N ₅ O ₄
312070	i-Pr	OMe	OMe	H	C ₂₂ H ₂₅ N ₅ O ₄
312071	t-Bu	OMe	OMe	H	C ₂₃ H ₂₇ N ₅ O ₄
312072	i-Pr	OMe	OMe	Cl	C ₂₂ H ₂₄ ClN ₅ O ₄
312073	cyclopropyl	OMe	H	H	C ₂₁ H ₂₁ N ₅ O ₃
312074	i-Pr	ethynyl	H	H	C ₂₂ H ₂₁ N ₅ O ₂
312075	4-[N(Me)2SO2NH]-Ph	OMe	OMe	H	C ₂₇ H ₂₉ N ₇ O ₆ S
312076	CH(Me)CH2OH	OMe	OMe	H	C ₂₂ H ₂₅ N ₅ O ₅
312294	1-Me-cyclopropyl	OMe	OMe	H	C ₂₃ H ₂₅ N ₅ O ₄

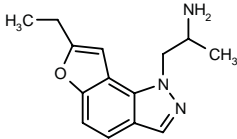
SOURCE – Novartis.

REFERENCES

1. Bhalay, G. et al. (Novartis AG;Novartis-Erfindungen VmbH) *8-Quinolinxanthine and 8-isoquinolinxanthine derivs. as PDE5 inhibitors.* WO 0177110.

312930

1-(7-Ethyl-1*H*-furo[2,3-*g*]indazol-1-yl)propan-2-amine



C14 H17 N3 O; Mol wt: 243.3083

ACTION – A representative compound from a series of furoindazole derivatives acting as highly selective 5-HT_{2C} receptor agonists. Compound gave an EC₅₀ of 1.0 nM when tested for agonist activity at 5-HT_{2C} receptors versus 93 nM for 5-HT_{2A} receptors. It induced erection in rats with an oral minimum effective dose (MED) of 0.3 mg/kg. Potentially useful for the treatment of sexual function disorders.

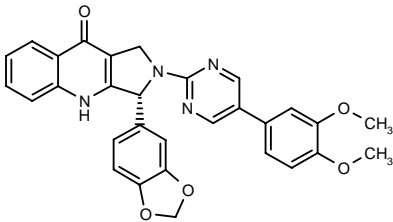
SOURCE – Yamanouchi.

REFERENCES

1. Goto, S. et al. (Yamanouchi Pharmaceutical Co., Ltd.) *Froindazole deriv.* WO 0183487.

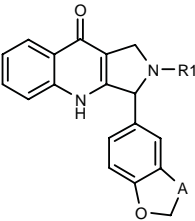
313242

3(*R*)-(1,3-Benzodioxol-5-yl)-2-[5-(3,4-dimethoxyphenyl)-pyrimidin-2-yl]-2,3,4,9-tetrahydro-1*H*-pyrrolo[3,4-*b*]-quinolin-9-one



C30 H24 N4 O5; Mol wt: 520.5426

ACTION – Agent with the ability to inhibit phosphodiesterase type 5 (PDE5; IC₅₀ = 0.075 nM) and thus potentially useful for the treatment of male and female sexual dysfunction including erectile dysfunction. Other exemplified pyrrolo[3,4-*b*]quinolinones are:



Compound	R1	A	Isomer	Formula
313244	4-Pyr-CH2OCO	O		C ₂₅ H ₁₉ N ₃ O ₅
313246	5-(2-Pyr)-2-pyrimidinyl	CH2	R	C ₂₈ H ₂₁ N ₅ O ₂
313248	5-(4-MeO-Ph)-2-pyrimidinyl	CH2	R	C ₃₀ H ₂₄ N ₄ O ₃
313249	5-[3,4-(MeO)2-Ph]-2-pyrimidinyl	O		C ₃₀ H ₂₄ N ₄ O ₅

SOURCE – Ortho-McNeil.

REFERENCES

1. Sui, Z. et al. (Ortho-McNeil Pharmaceutical, Inc.) *Substd. pyrrolopyridinone derivs. useful as phosphodiesterase inhibitors.* WO 0187882.

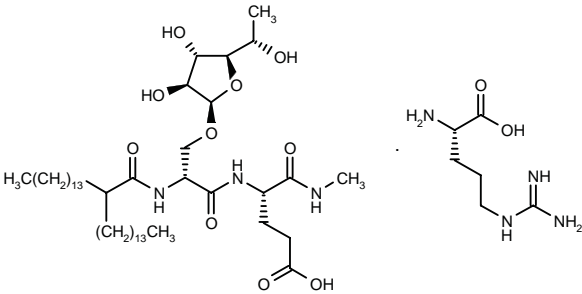
DERMATOLOGIC DRUGS

TREATMENT OF ALLERGIC SKIN DISORDERS

OJ-R9188

313494

N-(2-Tetradecylhexadecanoyl)-*O*-(α-*L*-fucofuranosyl)-*D*-seryl-*L*-glutamic acid methylamide *L*-arginine



C45 H85 N3 O10 . C6 H14 N4 O2; Mol wt: 1002.3800

ACTION – Low-molecular-weight selectin inhibitor (IC₅₀ = 4.3, 1.3 and 1.2 μM, respectively, for human E-, P- and L-selectin) proven to inhibit leukocyte infiltration in models of inflammation in mice such as thioglycollate-induced peritonitis, IgE-mediated skin reaction and picryl chloride-induced delayed-type hypersensitivity. In these models, compound given i.v. at doses of 3-10 mg/kg significantly reduced neutrophil and eosinophil infiltration into the tissues. Potentially useful for the treatment of allergic skin disorders.

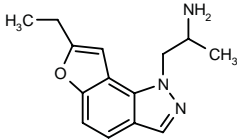
SOURCE – Novartis.

REFERENCES

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1-(7-Ethyl-1*H*-furo[2,3-*g*]indazol-1-yl)propan-2-amine



C14 H17 N3 O; Mol wt: 243.3083

ACTION – A representative compound from a series of furoindazole derivatives acting as highly selective 5-HT_{2C} receptor agonists. Compound gave an EC₅₀ of 1.0 nM when tested for agonist activity at 5-HT_{2C} receptors versus 93 nM for 5-HT_{2A} receptors. It induced erection in rats with an oral minimum effective dose (MED) of 0.3 mg/kg. Potentially useful for the treatment of sexual function disorders.

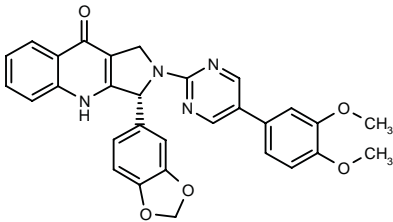
SOURCE – Yamanouchi.

REFERENCES

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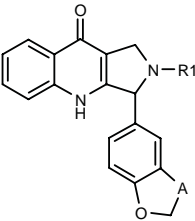
313242

3(*R*)-(1,3-Benzodioxol-5-yl)-2-[5-(3,4-dimethoxyphenyl)-pyrimidin-2-yl]-2,3,4,9-tetrahydro-1*H*-pyrrolo[3,4-*b*]-quinolin-9-one



C30 H24 N4 O5; Mol wt: 520.5426

ACTION – Agent with the ability to inhibit phosphodiesterase type 5 (PDE5; IC₅₀ = 0.075 nM) and thus potentially useful for the treatment of male and female sexual dysfunction including erectile dysfunction. Other exemplified pyrrolo[3,4-*b*]quinolinones are:



Compound	R1	A	Isomer	Formula
313244	4-Pyr-CH2OCO	O		C ₂₈ H ₁₉ N ₃ O ₅
313246	5-(2-Pyr)-2-pyrimidinyl	CH2	R	C ₂₈ H ₂₁ N ₅ O ₂
313248	5-(4-MeO-Ph)-2-pyrimidinyl	CH2	R	C ₃₀ H ₂₄ N ₄ O ₃
313249	5-[3,4-(MeO)2-Ph]-2-pyrimidinyl	O		C ₃₀ H ₂₄ N ₄ O ₅

SOURCE – Ortho-McNeil.

REFERENCES

1. Sui, Z. et al. (Ortho-McNeil Pharmaceutical, Inc.) *Substd. pyrrolopyridinone derivs. useful as phosphodiesterase inhibitors.* WO 0187882.

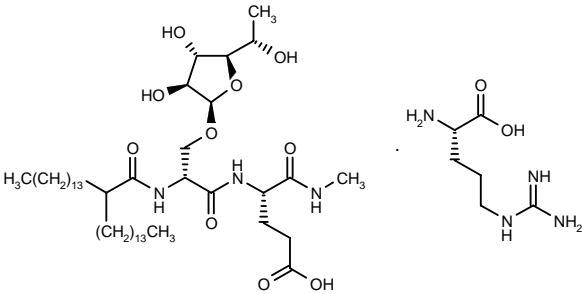
DERMATOLOGIC DRUGS

TREATMENT OF ALLERGIC SKIN DISORDERS

OJ-R9188

313494

N-(2-Tetradecylhexadecanoyl)-*O*-(α-*L*-fucofuranosyl)-*D*-seryl-*L*-glutamic acid methylamide *L*-arginine



C45 H85 N3 O10 . C6 H14 N4 O2; Mol wt: 1002.3800

ACTION – Low-molecular-weight selectin inhibitor (IC₅₀ = 4.3, 1.3 and 1.2 μM, respectively, for human E-, P- and L-selectin) proven to inhibit leukocyte infiltration in models of inflammation in mice such as thioglycollate-induced peritonitis, IgE-mediated skin reaction and picryl chloride-induced delayed-type hypersensitivity. In these models, compound given i.v. at doses of 3-10 mg/kg significantly reduced neutrophil and eosinophil infiltration into the tissues. Potentially useful for the treatment of allergic skin disorders.

SOURCE – Nippon Organon.

REFERENCES

1. Tsukida, T. et al. (Kanebo Pharmaceuticals, Ltd.) *Fucose derivs., drugs containing the same as active ingredient, and intermediates for producing the same.* EP 0859005, JP 1998109998, US 5919769, WO 9715585.

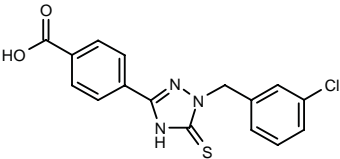
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3. Ikegami-Kuzuhara, A. et al. *Therapeutic potential of a novel synthetic selectin blocker, OJ-R9188, in allergic dermatitis.* Br J Pharmacol 2001, 134(7): 1498.

ANTIPSORIATICS

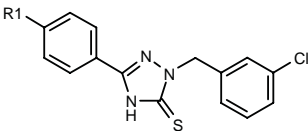
311999

4-[1-(3-Chlorobenzyl)-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl]benzoic acid

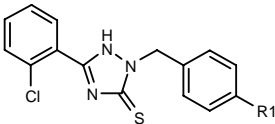


C16 H12 Cl N3 O2 S; Mol wt: 345.8088

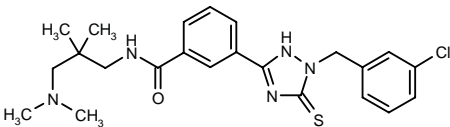
ACTION – Chemokine CXCR2 receptor modulator, reported to act as an antagonist at this receptor in neutrophils. Potentially useful for the treatment of psoriasis, chronic obstructive pulmonary disease (COPD) and disorders associated with CXCR2-mediated angiogenesis. Other specifically claimed 1,2,4-triazole-3-thione derivatives are:



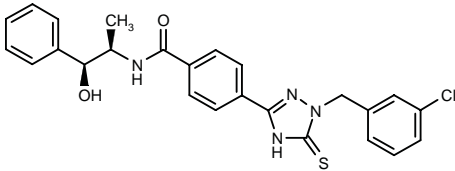
Compound	R1	Formula
312000	CON(Me)2	C ₁₈ H ₁₇ ClN ₄ OS
312002	4-(3-Cl-Ph)-1-Piz-CO	C ₂₆ H ₂₃ Cl ₂ N ₅ OS
312003	CONHSO2Ph	C ₂₂ H ₁₇ ClN ₄ O ₃ S ₂
312004	SO2NH2	C ₁₅ H ₁₃ ClN ₄ O ₂ S ₂



Compound	R1	Formula
312006	CONHCH2CN	C ₁₈ H ₁₄ ClN ₅ OS
312007	CONHCH2CH2F	C ₁₈ H ₁₆ ClFN ₄ OS



312005: C23 H28 Cl N5 O S



312001: C25 H23 Cl N4 O2 S

SOURCE – AstraZeneca.

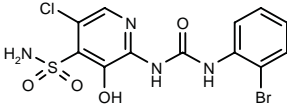
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312034

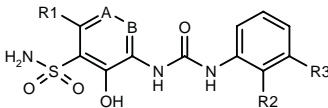
2-[3-(2-Bromophenyl)ureido]-5-chloro-3-hydroxypyridine-4-sulfonamide

N-(2-Bromophenyl)-*N*'-(5-chloro-3-hydroxy-4-sulfamoylpyridin-2-yl)urea



C12 H10 Br Cl N4 O4 S; Mol wt: 421.6580

ACTION – An inhibitor of the binding of IL-8 and other chemokines (namely GRO α , GRO β , GRO γ , NAP-2 and ENA-78) to IL-8 α (CXCR1) and IL-8 β (CXCR2) receptors. Potentially useful for the treatment of a wide variety of IL-8 receptor-mediated conditions including psoriasis, atopic dermatitis, arthritis, asthma, chronic obstructive pulmonary disease, adult respiratory distress syndrome, inflammatory bowel disease, Crohn's disease, ulcerative colitis, stroke, septic shock, multiple sclerosis, cardiac and renal reperfusion injury, glomerulonephritis, thrombosis, transplant rejection, Alzheimer's disease, atherosclerosis, osteoporosis, viral infections, angiogenesis, etc. Other specifically claimed diaryl urea derivatives are:



Compound	R1	R2	R3	A	B	Formula
312035	Cl	Cl	Cl	CH	N	C ₁₂ H ₉ Cl ₃ N ₄ O ₄ S
312036	Cl	Br	H	N	CH	C ₁₂ H ₁₀ BrClN ₄ O ₄ S
312037	Cl	Cl	Cl	N	CH	C ₁₂ H ₉ Cl ₃ N ₄ O ₄ S
312038	Cl	Br	H	N	N	C ₁₁ H ₉ BrClN ₅ O ₄ S
312039	Cl	Cl	Cl	N	N	C ₁₁ H ₈ Cl ₃ N ₅ O ₄ S
312040	CN	Br	H	CH	N	C ₁₃ H ₁₀ BrN ₅ O ₄ S
312041	CN	Cl	Cl	CH	N	C ₁₃ H ₉ Cl ₂ N ₅ O ₄ S
312042	CN	Br	H	N	CH	C ₁₃ H ₁₀ BrN ₅ O ₄ S
312043	CN	Cl	Cl	N	CH	C ₁₃ H ₉ Cl ₂ N ₅ O ₄ S
312044	CN	Br	H	N	N	C ₁₂ H ₉ BrN ₆ O ₄ S
312045	CN	Cl	Cl	N	N	C ₁₂ H ₈ Cl ₂ N ₆ O ₄ S

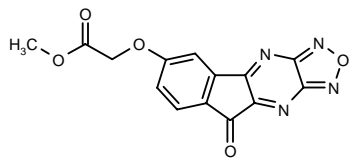
SOURCE – GlaxoSmithKline.

REFERENCES

1. Palovich, M.R. et al. (GlaxoSmithKline Inc.) *IL-8 receptor antagonists.* WO 0176530.

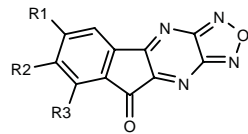
312250

2-(9-Oxo-9*H*-indeno[1,2-*b*][1,2,5]oxadiazolo[3,4-*e*]-pyrazin-6-yloxy)acetic acid methyl ester



C14 H8 N4 O5; Mol wt: 312.2402

ACTION – IL-8 (CXCR1 or CXCR2) receptor antagonist with potential in the treatment of chemokine-mediated conditions including psoriasis, atopic dermatitis, cancer, asthma, chronic obstructive pulmonary disease, adult respiratory distress syndrome, arthritis, inflammatory bowel disease, Crohn’s disease, ulcerative colitis, gastric ulcer, septic shock, stroke, atherosclerosis, cardiac and renal reperfusion injury, thrombosis, Alzheimer’s disease and transplant rejection. Other specifically claimed tetracyclic compounds include the following:



Compound	R1	R2	R3	Formula
312251	H	Br	H	C ₁₁ H ₃ BrN ₄ O ₂
312253	H	H	OH	C ₁₁ H ₄ N ₄ O ₃
312254	H	H	OCH ₂ Ac	C ₁₄ H ₈ N ₄ O ₄
312255	H	H	3-Pyr-CH ₂ O	C ₁₇ H ₉ N ₅ O ₃
312256	CH(Me)OMe	H	H	C ₁₄ H ₁₀ N ₄ O ₃

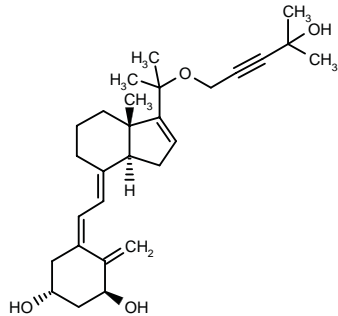
SOURCE – Pfizer.

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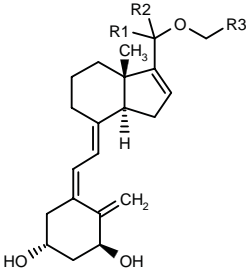
312805

(1*S*,3*R*,5*Z*,7*E*,20*S*)-20-(4-Hydroxy-4-methyl-2-pentynyloxy)-20-methyl-9,10-secopregna-5,7,10,16-tetraene-1,3-diol



C28 H40 O4; Mol wt: 440.6200

ACTION – A vitamin D₃ analogue with potential in the treatment of skin disorders such as psoriasis. Compound was shown to be 23-fold more active than the reference compound 1 α ,25(OH)₂-D₃ in inhibiting the proliferation of human keratinocytes *in vitro*. Other exemplified compounds include the following:



Compound	R1	R2	R3	Formula
312806	H	H	(<i>E</i>)-CH=CHC(Et)2OH	C ₂₈ H ₄₂ O ₄
312807	Me	Me	ethynylene-CH(Et)2OH	C ₃₀ H ₄₄ O ₄

SOURCE – Chugai.

REFERENCES

1. Kawase, A. et al. (Chugai Pharmaceutical Co. Ltd.) *Vitamin D derivs*. WO 0179166.

ALEFACEPT

Prop INN; USAN

197339

Recombinant human LFA-3/IgG₁ fusion protein

1-92-LFA-3 (antigen) (human) fusion protein with immunoglobulin G₁ (human hinge-C(H)₂-C(H)₃ γ 1-chain), dimer

BG-9273
BG-9712
LFA3TIP
LFA-3(92)IgG
Amevive™

ACTION – Antipsoriatic agent, a recombinant LFA-3/IgG human fusion protein that binds to T-cells and blocks their activation and proliferation, and also induces selective T-cell apoptosis. Compound was shown to inhibit the mixed lymphocyte reaction in human peripheral blood lymphocytes (PBLs) induced by human JY B-cell tumor cells. Compound also inhibited tetanus toxoid-hepatitis B surface antigen-, anti-CD3 MAb- and phytohemagglutinin (PHA)-induced T-cell proliferation in murine A20 cells PBLs. Moreover, a dose of 100 μ g i.p. inhibited PHA-induced T-cell proliferation in mice. In phase II and phase III clinical trials in patients with psoriasis, it selectively and consistently reduced circulating memory-effector T-cells and activated interferon gamma-producing T-cells in psoriatic lesions, which was associated with clinical improvement. Patients maintain their ability to mount an immune response to new and previously encountered antigens, suggesting that it targets pathogenic T-cells but avoids general immunosuppression. Compound was very well tolerated, nonimmunogenic and was not associated with rebound.

SOURCE – Biogen.

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19. Goedkoop, A.Y. et al. *Alefacept reduces synovial inflammatory infiltrate and improves outcome in psoriatic arthritis*. 60th Annu Meet Am Acad Dermatol (Feb 22-27, New Orleans) 2002, Abst P582.

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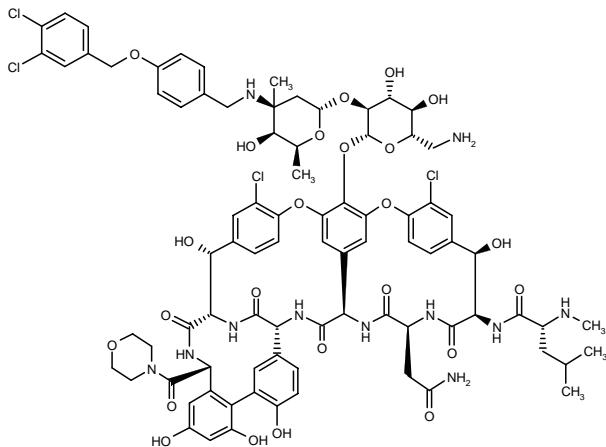
MONOGRAPH – Sorbera, L.A. et al. *Alefacept.* Drugs Fut 2001, 26(6): 0527.

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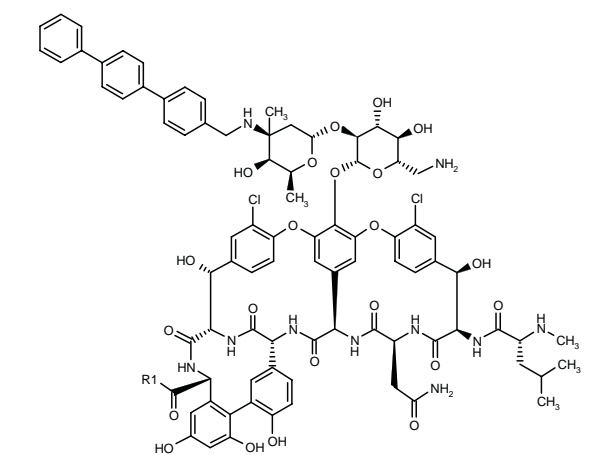
312594

6'-Amino-6'-deoxy-3''-N-[4-(3,4-dichlorobenzoyloxy)-benzyl]vancomycin 4-morpholinylamide



C84 H93 Cl4 N11 O24; Mol wt: 1782.5240

ACTION – Glycopeptide derivative with antibacterial activity, particularly useful for the treatment of infections caused by methicillin-resistant staphylococci and enterococci including vancomycin-resistant enterococci. Other exemplified vancomycin analogues include the following:



Compound	R1	Formula
312595	4-morpholinyl	C ₈₉ H ₉₇ Cl ₂ N ₁₁ O ₂₃
312596	NH(CH ₂ CH ₂ O)3CH ₂ CH ₂ N3	C ₉₃ H ₁₀₆ Cl ₂ N ₁₄ O ₂₅

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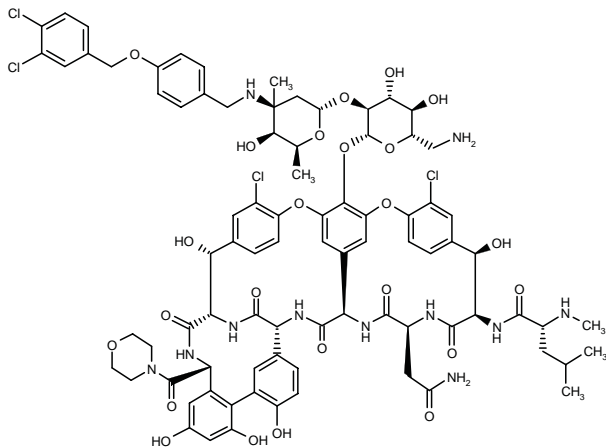
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ANTIINFECTIVE THERAPY

ANTIBIOTICS

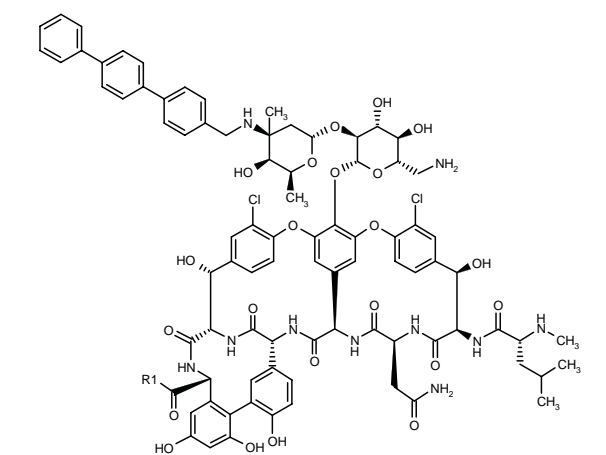
312594

6'-Amino-6'-deoxy-3''-N-[4-(3,4-dichlorobenzoyloxy)-benzyl]vancomycin 4-morpholinylamide

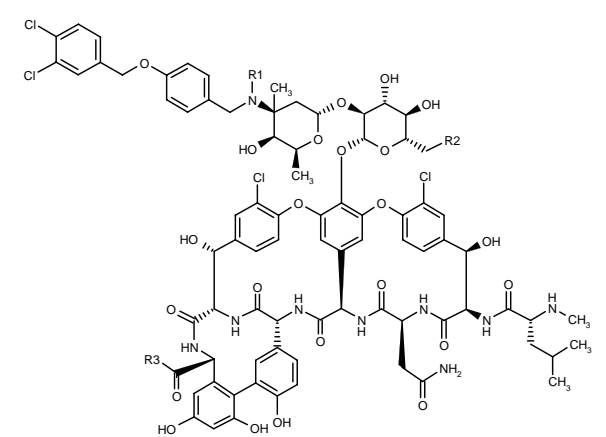


C84 H93 Cl4 N11 O24; Mol wt: 1782.5240

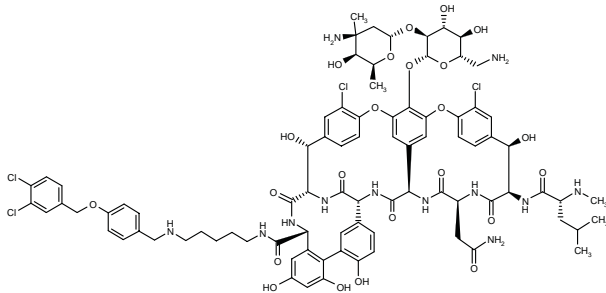
ACTION – Glycopeptide derivative with antibacterial activity, particularly useful for the treatment of infections caused by methicillin-resistant staphylococci and enterococci including vancomycin-resistant enterococci. Other exemplified vancomycin analogues include the following:



Compound	R1	Formula
312595	4-morpholinyl	C ₈₉ H ₉₇ Cl ₂ N ₁₁ O ₂₃
312596	NH(CH ₂ CH ₂ O) ₃ CH ₂ CH ₂ N ₃	C ₉₃ H ₁₀₆ Cl ₂ N ₁₄ O ₂₅



Compound	R1	R2	R3	Formula
312597	H	4-morpholinyl	4-morpholinyl	C ₈₈ H ₉₈ Cl ₄ N ₁₁ O ₂₅
312598	H	NHCH ₂ CH ₂ OH	NH(CH ₂) ₃ N(Me) ₂	C ₈₇ H ₁₀₂ Cl ₄ N ₁₂ O ₂₄
312599	H	1-Piz	NH(CH ₂) ₃ N(Me) ₂	C ₈₉ H ₁₀₅ Cl ₄ N ₁₃ O ₂₃
312600	allyl	NH ₂	allyl-O	C ₈₆ H ₉₄ Cl ₄ N ₁₀ O ₂₄
312601	H	NH ₂	NH(CH ₂) ₃ N(Me) ₂	C ₈₅ H ₉₈ Cl ₄ N ₁₂ O ₂₃



312602: C85 H98 Cl4 N12 O23

SOURCE – Merck & Co.

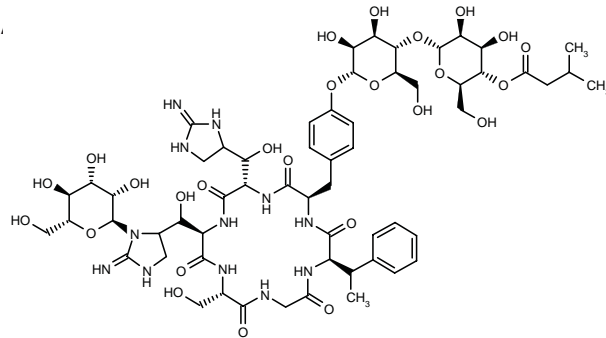
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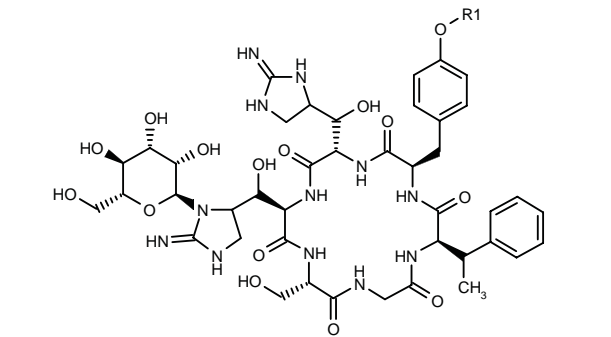
313077

(3*S*,6*R*,9*S*,12*R*,15*R*)-9-[(*R*)-Hydroxy(2-iminoimidazolidin-4-yl)methyl]-6-[(*S*)-hydroxy-[2-imino-3-(α -D-mannopyranosyl)imidazolidin-4-yl]methyl]-3-(hydroxymethyl)-12-[4-[4-*O*-(3-methylbutanoyl)- α -D-mannopyranosyl-(1-4)- α -D-mannopyranosyloxy]benzyl]-15-[1(*S*)-phenylethyl]-1,4,7,10,13,16-hexaazacyclooctadecane-2,5,8,11,14,17-hexone



C59 H86 N12 O26; Mol wt: 1379.3860

ACTION – Cyclic glycopeptide antibiotic produced by *Streptomyces hygroscopicus*, active against Gram-positive bacteria including methicillin-susceptible and -resistant *Staphylococcus aureus* (MIC = 4 μ g/ml) and coagulase-negative staphylococci (MIC = 2-4 μ g/ml). Compound showed bactericidal activity against *S. aureus* and appears to target the bacterial cell wall. In mice with systemic infections caused by *S. aureus*, compound exhibited efficacy comparable to vancomycin (ED₅₀ = 0.59 and 0.94 mg/kg i.v., respectively). Other related compounds are:



Compound	R1	Formula
AC-98-1 [313073]	4-O-(α -D-mannopyranosyl)- α -D-mannopyranosyl	C ₅₄ H ₇₈ N ₁₂ O ₂₅
AC-98-2 [313074]	H	C ₄₂ H ₅₈ N ₁₂ O ₁₅
AC-98-3 [313075]	4-O-[2-O-(<i>i</i> -BuCOO)- α -D-mannopyranosyl]- α -D-mannopyranosyl	C ₅₉ H ₈₆ N ₁₂ O ₂₆
AC-98-4 [313076]	4-O-[3-O-(<i>i</i> -BuCOO)- α -D-mannopyranosyl]- α -D-mannopyranosyl	C ₅₉ H ₈₆ N ₁₂ O ₂₆

SOURCE – Wyeth Pharmaceuticals.

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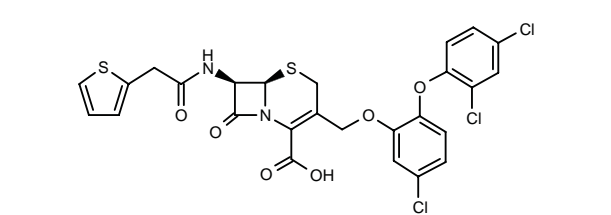
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LAMECTACIN

291858

(6*R*,7*R*)-3-[5-Chloro-2-(2,4-dichlorophenoxy)-phoxymethyl]-7-[2-(2-thienyl)acetamido]-3-cephem-4-carboxylic acid

NB-2001



C26 H19 Cl3 N2 O6 S2; Mol wt: 625.9351

ACTION – Cephalosporin antibiotic designed to release the bactericide triclosan in the presence of β -lactamase; it also acts as a conventional antibiotic in nonresistant bacteria, blocking bacterial cell wall synthesis. Compound exhibited superior potency compared to other antibiotics against a range of Gram-positive and Gram-negative bacteria including methicillin-resistant *Staphylococcus aureus* (MRSA), *Staphylococcus epidermidis*, *Streptococcus pneumoniae*, *Moraxella catarrhalis* and *Haemophilus influenzae*, as well as vancomycin-resistant enterococci, *Klebsiella pneumoniae*, *Enterobacter aerogenes* and *Enterobacter cloacae*. Moreover, compound was seen to protect mice from systemic infections induced by MRSA.

SOURCE – NewBiotics.

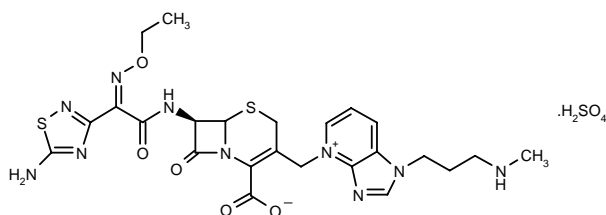
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S-3578

312464

7(R)-[2-(5-Amino-1,2,4-thiadiazol-3-yl)-2(Z)-(ethoxyimino)acetamido]-3-[1-[3-(methylamino)propyl]-1H-imidazo[4,5-b]pyridin-4-iumylmethyl]-3-cephem-4-carboxylate sulfate



C24 H28 N10 O5 S2 . H2 O4 S; Mol wt: 698.7600

ACTION – Broad-spectrum cephalosporin active against clinical isolates of Gram-positive and Gram-negative bacteria including methicillin-resistant *Staphylococcus aureus* (MRSA; MIC₉₀ = 4 μ g/ml), methicillin-resistant *Staphylococcus epidermidis* (MIC₉₀ = 2 μ g/ml), penicillin-resistant *Streptococcus pneumoniae* (MIC = 0.5-2 μ g/ml), *Pseudomonas aeruginosa* and *Moraxella catarrhalis*. Compound exhibited affinity for penicillin-binding proteins PBP1A, PBP3 and PBP4 of *P. aeruginosa* (IC₅₀ = 0.34, 0.31, 0.43 μ g/ml, respectively), as well as for PBP1 and PBP2 of *S. aureus* (IC₅₀ = 0.28 and 0.34 μ g/ml, respectively), and it was stable to chromosomal β -lactamases. In experimental murine infections caused by Gram-

positive and Gram-negative bacteria, compound was effective against systemic infections caused by MRSA (ED₅₀ = 7.21-8.91 mg/kg s.c.); potent efficacy was also demonstrated against subcutaneous infections caused by methicillin-sensitive and -resistant *S. aureus*. In contrast to ceftazidime and linezolid, compound was effective against polymicrobial systemic infections caused by MRSA and *P. aeruginosa* (ED₅₀ = 10.2 mg/kg s.c.), and it was also effective against polymicrobial pulmonary infections, pulmonary infections caused by penicillin-resistant *S. pneumoniae* and urinary tract infections caused by *P. aeruginosa*. Compound exhibited a favorable pharmacokinetic profile, similar to that of ceftazidime and cefepime in rats, mice and monkeys following i.v. administration of a dose of 20 mg/kg; it entered the cerebrospinal fluid of newborn rats at a rate of 20.2%, but the transport rate into inflamed granuloma pouch exudates in rats was about 3 times higher (68.3%).

SOURCE – Shionogi.

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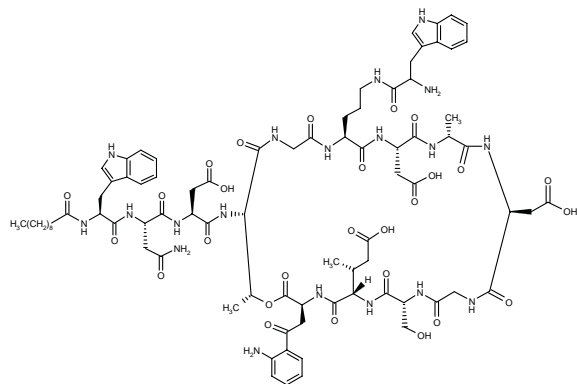
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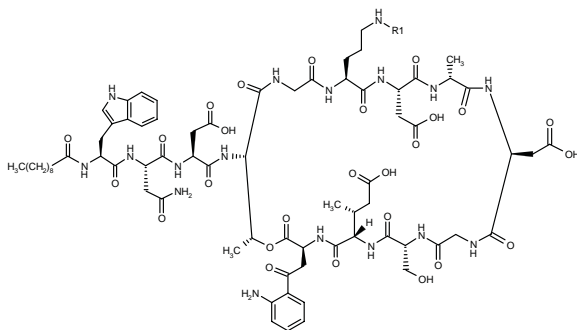
N-Decanoyl-L-tryptophyl-L-asparaginyl-L-aspartyl-L-threonyl-glycyl-*N*^δ-(DL-tryptophyl)-L-ornithyl-L-aspartyl-D-alanyl-L-aspartyl-glycyl-D-seryl-threo-3-methyl-L-glutamyl-γ-(2-aminophenyl)-γ-oxo-L-α-aminobutyric acid *C*-1.13-*O*-2.4-lactone

6-(*N*⁵-DL-Tryptophyl-L-ornithine)daptomycin



C83 H111 N19 O27; Mol wt: 1806.8960

ACTION – Antibacterial agent, a lipopeptide analogue of daptomycin with excellent *in vitro* activity against Gram-positive bacteria including *Staphylococcus aureus*, methicillin-resistant *S. aureus* (MRSA), *Enterococcus faecium* and *Enterococcus faecalis* (MIC = 0.78, 0.78, 1.56 and 3.1 µg/ml, respectively). *In vivo* in a mouse MRSA septicemia model, compound dose-dependently (0.1-2.5 mg/kg s.c.) increased survival rate and its activity was comparable to that of daptomycin. It exhibited favorable pharmacokinetics, with a *C*_{max} of 258 µg/ml and a half-life of 2.8 h. Other related compounds are:



Compound	R1	Formula
306846	2,3,4,9-tetrahydro-1H-beta-carbolin-3-yl-CO	C ₈₄ H ₁₁₁ N ₁₉ O ₂₇
306847	C(=NH)NH2	C ₇₃ H ₁₀₃ N ₁₉ O ₂₆
313093	H-L-Lys-	C ₇₈ H ₁₁₃ N ₁₉ O ₂₇

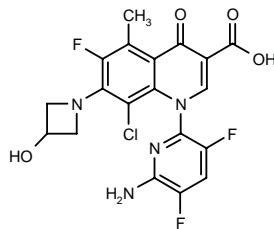
SOURCE – Cubist Pharmaceuticals.

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1. Hill, J. et al. (Cubist Pharmaceuticals, Inc.) *Lipopeptides as antibacterial agents*. WO 0144274.
2. Hill, J.M. et al. *Novel lipopeptides 1: Synthesis and biological activity of ornithine amino amide analogs of daptomycin*. 41st Intersci Conf Antimicrob Agents Chemother (Dec 16-19, Chicago) 2001, Abst F-1150.

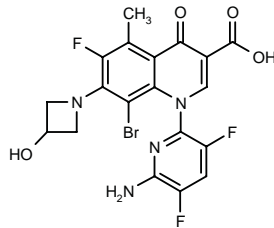
310269

1-(6-Amino-3,5-difluoropyridin-2-yl)-8-chloro-6-fluoro-7-(3-hydroxyazetidin-1-yl)-5-methyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid



C19 H14 Cl F3 N4 O4; Mol wt: 454.7906

ACTION – Quinolone antibacterial agent, particularly useful for the prevention and treatment of infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA), with MIC values of < 0.003 µg/ml against a panel of MRSA strains. *In vivo*, it produced no convulsions or deaths following i.v. administration to mice at 100 mg/kg. Another exemplified 4-oxoquinoline-3-carboxylic acid is:



310270: C19 H14 Br F3 N4 O4

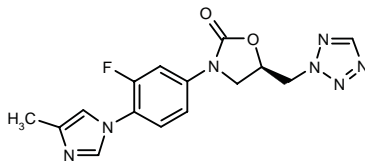
SOURCE – Dainippon Pharmaceutical.

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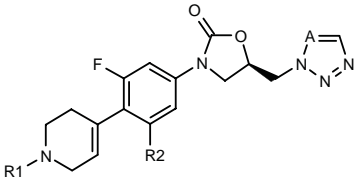
312497

3-[3-Fluoro-4-(4-methyl-1*H*-imidazol-1-yl)phenyl]-5(*R*)-(2*H*-tetrazol-2-ylmethyl)oxazolidin-2-one

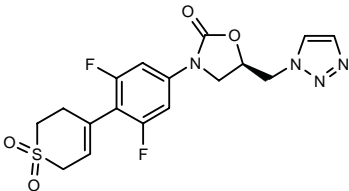


C15 H14 F N7 O2; Mol wt: 343.3206

ACTION – Oxazolidinone antibacterial agent active against Gram-positive and Gram-negative bacteria including MRSA (methicillin-resistant *Staphylococcus aureus*) and MRCNS (methicillin-resistant coagulase-negative staphylococci), and particularly against vancomycin-resistant strains and *Enterococcus faecium* strains resistant to aminoglycosides and β -lactams. Other exemplified compounds are:



Compound	R1	R2	A	Formula
312499	COCH2OH	F	CH	C ₁₉ H ₁₉ F ₂ N ₅ O ₄
312500	(S)-COCH(OH)CH2OH	F	CH	C ₂₀ H ₂₁ F ₂ N ₅ O ₅
312501	COCH2OH	H	CH	C ₁₉ H ₂₀ FN ₅ O ₄
312502	(S)-COCH(OH)CH2OH	H	CH	C ₂₀ H ₂₂ FN ₅ O ₅
312503	(R)-COCH(OH)CH2SMe	H	CH	C ₂₁ H ₂₄ FN ₅ O ₄ S
312504	COCH2OH	H	N	C ₁₈ H ₁₉ FN ₆ O ₄



312498: C17 H16 F2 N4 O4 S

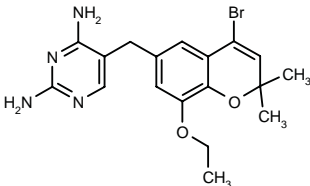
SOURCE – AstraZeneca.

REFERENCES

1. Gravestock, M.B. et al. (AstraZeneca AB;AstraZeneca plc) *Oxazolidinone derivs. with antibiotic activity*. WO 0181350.

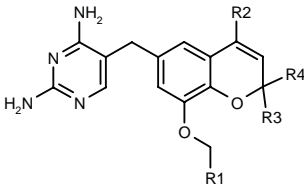
312752

5-(4-Bromo-8-ethoxy-2,2-dimethyl-2*H*-1-benzopyran-6-ylmethyl)pyrimidine-2,4-diamine



C18 H21 Br N4 O2; Mol wt: 405.2939

ACTION – Antibacterial agent giving an MIC of 0.5 μ g/ml against *Streptococcus pneumoniae* 1/1 and also reported to demonstrate *in vitro* activity against other bacteria including antibiotic-resistant strains. Other specifically claimed pyrimidinylmethyl-chromenes are:



Compound	R1	R2	R3	R4	Formula
312753	H	Br	Me	Me	C ₁₇ H ₁₉ BrN ₄ O ₂
312754	H	Br	-CH2CH2OCH2CH2-		C ₁₉ H ₂₁ BrN ₄ O ₃
312755	Me	Me	Me	Me	C ₁₉ H ₂₄ N ₄ O ₂
312756	H	Cl	Me	Me	C ₁₇ H ₁₉ ClN ₄ O ₂
312757	Me	Et	Me	Me	C ₂₀ H ₂₆ N ₄ O ₂
312758	H	SMe	Me	Me	C ₁₈ H ₂₂ N ₄ O ₂ S
312759	Me	Pr	Me	Me	C ₂₁ H ₂₈ N ₄ O ₂
312760	H	MeOCH2-ethynylene	Me	Me	C ₂₁ H ₂₄ N ₄ O ₃
312761	H	4-F-Ph	Me	Me	C ₂₃ H ₂₃ FN ₄ O ₂
312762	H	Br	-(CH2)3-		C ₁₈ H ₁₉ BrN ₄ O ₂

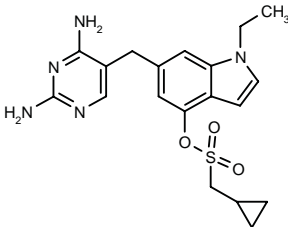
SOURCE – Roche.

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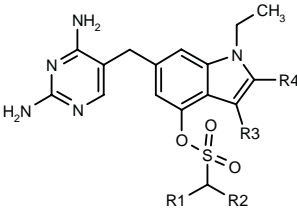
312763

Cyclopropylmethanesulfonic acid 6-(2,4-diaminopyrimidin-5-ylmethyl)-1-ethyl-1*H*-indol-4-yl ester



C19 H23 N5 O3 S; Mol wt: 401.4887

ACTION – Antibacterial agent giving an MIC of 1 μ g/ml against *Streptococcus pneumoniae* 1/1 and also reported to demonstrate *in vitro* activity against other bacteria including antibiotic-resistant strains. Other specifically claimed pyrimidinylmethyl-indoles are:



Compound	R1	R2	R3	R4	Formula
312764	i-Pr	H	H	H	C ₁₉ H ₂₅ N ₅ O ₃ S
312765	Et	Me	H	H	C ₁₉ H ₂₅ N ₅ O ₃ S
312766	cyclopropyl	H	Me	H	C ₂₀ H ₂₅ N ₅ O ₃ S
312767	Et	Me	H	Me	C ₂₀ H ₂₇ N ₅ O ₃ S

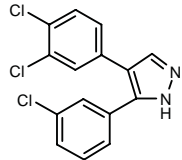
SOURCE – Roche.

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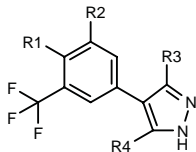
312768

5-(3-Chlorophenyl)-4-(3,4-dichlorophenyl)-1*H*-pyrazole

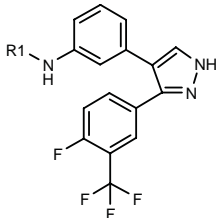


C15 H9 Cl3 N2; Mol wt: 323.6091

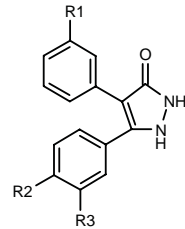
ACTION – Antibacterial agent, an inhibitor of bacterial RNA polymerase, as demonstrated *in vitro* against *Escherichia coli* RNA polymerase. Compound gave MIC values below 500 µM against a panel of bacterial strains. Other exemplified pyrazole derivatives are:



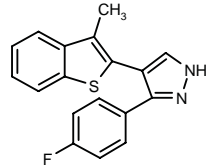
Compound	R1	R2	R3	R4	Formula
312769	Cl	H	H	3-Cl-Ph	C ₁₆ H ₉ Cl ₂ F ₃ N ₂
312770	Cl	H	H	Ph	C ₁₆ H ₁₀ ClF ₃ N ₂
312771	F	H	H	4-F-Ph	C ₁₆ H ₉ F ₃ N ₂
312772	3-(EtNH)- -1-pyrrolidinyl	H	H	4-F-Ph	C ₂₂ H ₂₂ F ₄ N ₄
312773	1-Piz- -CH ₂ CH ₂ NH	H	H	4-F-Ph	C ₂₂ H ₂₃ F ₄ N ₅
312774	PhCH ₂ NH- CH ₂ CH ₂ NH	H	H	4-F-Ph	C ₂₆ H ₂₂ F ₄ N ₄
312775	4-(SO ₂ NH ₂)- -PhCH ₂ CH ₂ NH	H	H	4-F-Ph	C ₂₄ H ₂₀ F ₄ N ₄ O ₂ S
312776	3-NH ₂ - -1-pyrrolidinyl	H	H	4-F-Ph	C ₂₀ H ₁₈ F ₄ N ₄
312777	H	F	H	4-F-Ph	C ₁₆ H ₉ F ₅ N ₂
312778	H	NHCH ₂ - CH ₂ NH ₂	H	4-F-Ph	C ₁₈ H ₁₆ F ₄ N ₄



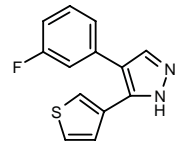
Compound	R1	Formula
312779	H	C ₁₆ H ₁₁ F ₄ N ₃
312781	SO ₂ Me	C ₁₇ H ₁₃ F ₄ N ₃ O ₂ S



Compound	R1	R2	R3	Formula
312783	H	H	CF ₃	C ₁₆ H ₁₁ F ₃ N ₂ O
312784	CF ₃	Cl	H	C ₁₆ H ₁₀ ClF ₃ N ₂ O



312785: C18 H13 F N2 S



312786: C13 H9 F N2 S

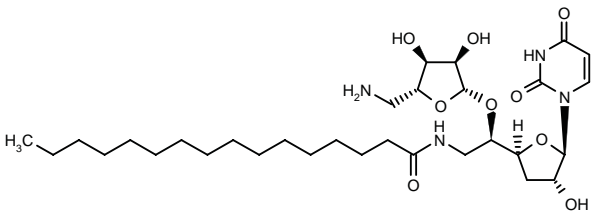
SOURCE – Tularik.

REFERENCES

1. Li, L. et al. (Tularik Inc.) *Pyrazole antimicrobial agents.* WO 0182930.

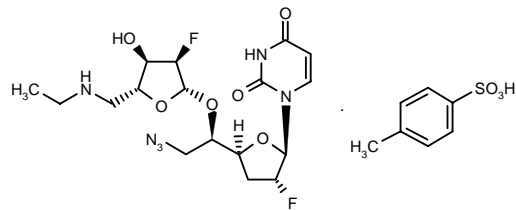
312812

5'-*O*-(5-Amino-5-deoxy-β-D-ribofuranosyl)-3'-deoxy-5'(*R*)-*C*-(hexadecanamidomethyl)uridine



C31 H54 N4 O9; Mol wt: 626.7866

ACTION – Antibacterial agent with activity against Gram-positive microorganisms including staphylococci, streptococci, pneumococci and enterococci, i.e., *Staphylococcus aureus*, *Streptococcus pyogenes* and *Enterococcus faecium*. Another exemplified uridine derivative is:



312814: C17 H24 F2 N6 O6 . C7 H8 O3 S

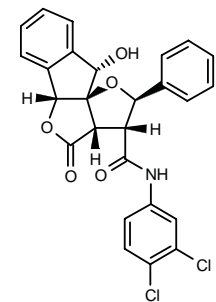
SOURCE – Aventis Pharma.

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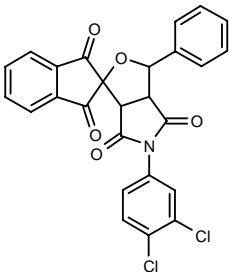
313065^{2,3}

(2*R**,3*R**,3*aS**,5*aR**,10*S**,10*aR**)-*N*-(3,4-Dichlorophenyl)-10-hydroxy-4-oxo-2-phenyl-2,3,3*a*,4,5*a*,10-hexahydrofuro[2,3-*c*]indeno[1,2-*b*]furan-3-carboxamide



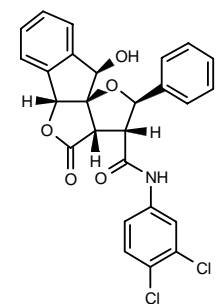
C26 H19 Cl2 N O5; Mol wt: 496.3441

ACTION – Antibacterial agent, a selective inhibitor of *Staphylococcus aureus* and *Enterococcus faecalis* phenylalanine–tRNA ligase (IC₅₀ = 0.81 and 0.37 μM, respectively), but inactive against human enzyme at up to 100 μM. Compound exhibited good antibacterial activity against *S. aureus* with an MIC value of 3.1 μg/ml. This compound is derived from **CB-126229**, the *trans*-isomer of **CB-102930**, both potent but unstable enzyme inhibitors.



Compound	Isomer	Formula
CB-126229 ^{*,1,3} [288177]	3'R*,3'aR*,6'aS*	C ₂₆ H ₁₅ Cl ₂ NO ₅
CB-102930 ^{*,1,3} [288178]	3'R*,3'aS*,6'aR*	C ₂₆ H ₁₅ Cl ₂ NO ₅

Another related compound with enzyme inhibitory (IC₅₀ = 0.47-0.51 μM) and antibacterial activity against *S. aureus* (MIC = 6.25 μg/ml) is:



313066^{2,3}: C26 H19 Cl2 N O5

SOURCE – Cubist Pharmaceuticals.

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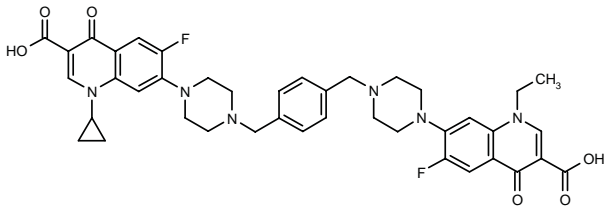
2. Finn, J. et al. (Cubist Pharmaceuticals, Inc.) *Tetracyclic heterocycles as antimicrobial agents*. US 6153645, WO 0017206.

3. Hill, J.M. et al. *Synthesis and activity of spirocyclic tetrahydrofurans as inhibitors of phenylalanine tRNA synthetase*. 41st Intersci Conf Antimicrob Agents Chemother (Dec 16-19, Chicago) 2001, Abst F-1707.

*Identified compound **288177** Drug Data Rep 2000, 022(07): 0621.
Identified compound **288178 (see **288177**) Drug Data Rep 2000, 022(07): 0621.

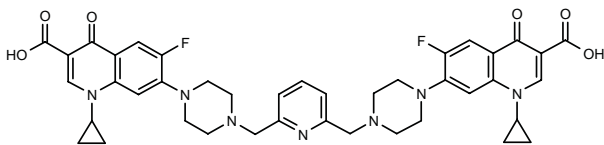
313578

7-[4-[4-[4-(3-Carboxy-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinolin-7-yl)piperazin-1-ylmethyl]benzyl]-piperazin-1-yl]-1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid



C41 H42 F2 N6 O6; Mol wt: 752.8148

ACTION – Antibacterial agent, a piperazinyl-linked fluoroquinolone with strong antibacterial activity against Gram-positive and Gram-negative bacteria including *Staphylococcus aureus* (MIC < 0.03 μg/ml), glycopeptide intermediately susceptible *S. aureus* (MIC = 4 μg/ml), methicillin-resistant *S. aureus* (MRSA; MIC < 0.03 μg/ml) and ciprofloxacin- or penicillin-resistant *Streptococcus pneumoniae* (MIC = 0.5-4 μg/ml). Compound did not interfere with norA-mediated efflux of ethidium bromide, suggesting that is not a substrate for this pump. Another related compound is:



313580: C41 H41 F2 N7 O6

SOURCE – Wayne State University, Detroit, MI (US).

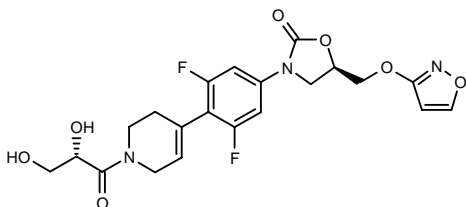
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AZD-2563*

284303

3-[4-[1-[2(*S*),3-Dihydroxypropionyl]-1,2,3,6-tetrahydropyridin-4-yl]-3,5-difluorophenyl]-5(*R*)-(isoxazol-3-yloxy-methyl)oxazolidin-2-one



C21 H21 F2 N3 O7; Mol wt: 465.4069

ACTION – Oxazolidinone antibacterial active against Gram-positive pathogens including multidrug-resistant *Staphylococcus aureus*, vancomycin-resistant enterococci and penicillin/macrolide-resistant *Streptococcus pneumoniae* (MIC = 0.25-4 µg/ml). The activity of compound was equal or slightly higher than that of linezolid and was not affected by resistance to other classes of antibacterial agents, pH, inoculum size or the presence of serum; its activity was mainly bacteriostatic. Compound was also active against unusual Gram-positive species and anaerobes such as *Corynebacterium* spp., *Listeria* spp., *Micrococcus* spp., *Bacillus* spp. and *Stomatococcus mucilaginosus* at concentrations of 4 µg/ml or less, and it was slightly more potent than linezolid. In mice with systemic infections caused by multiple bacterial pathogens including antibiotic-resistant strains of *S. pneumoniae* and *S. aureus*, compound exhibited strong and time-dependent bacteriostatic efficacy and produced more persistent effects than linezolid. The bacteriostatic dose was not affected by the dosing interval, suggesting the feasibility of once-daily dosing in man.

SOURCE – AstraZeneca.

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13. Johnson, A.P. et al. *In vitro activity of a novel oxazolidinone, AZD2563, against Gram-positive cocci, including diverse multi-resistant isolates*. 41st Intersci Conf Antimicrob Agents Chemother (Dec 16-19, Chicago) 2001, Abst F-1026.

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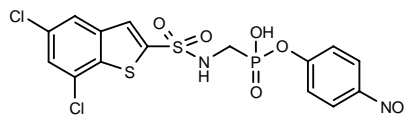
21. AstraZeneca takes an ambitious approach to drug R&D. DailyDrugNews.com (Daily Essentials) 1999, Dec 13.

*Identified compound **284303** (see **284302**) Drug Data Rep 2000, 022(03): 0261.

MG-2394

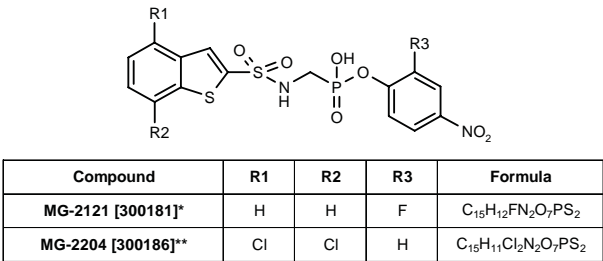
312526

5,7-Dichloro-1-benzothien-2-ylsulfonamidomethylphosphonic acid 4-nitrophenyl monoester



C15 H11 Cl2 N2 O7 P S2; Mol wt: 497.2709

ACTION – Potent, irreversible and selective non-β-lactam inhibitor of class A and C β-lactamases (IC₅₀ = 0.2 and 87 µM, respectively) active *in vitro* against β-lactamase-producing microorganisms. *In vivo* in mouse models of sepsis caused by class C-expressing *Enterobacter cloacae*, compound in combination with ceftioxone afforded 60% survival compared to only 7% survival in mice treated with the combination of tazobactam and the antibiotic. Other related compounds are:



SOURCE – MethylGene.

REFERENCES

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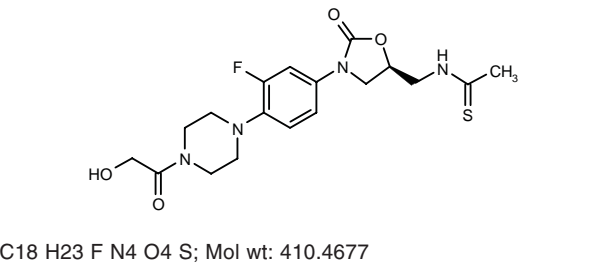
*Identified compound **300181** Drug Data Rep 2001, 023(06): 0573.

Identified compound **300186 (see **300181**) Drug Data Rep 2001, 023(06): 0573.

PNU-173995*

272072

N-[3-[3-Fluoro-4-[4-(2-hydroxyacetyl)piperazin-1-yl]-phenyl]-2-oxooxazolidin-5(S)-ylmethyl]thioacetamide



ACTION – Oxazolidinone thioamide antibacterial agent with moderate clearance in both rats and monkeys and higher clearance in dogs; the oral bioavailability was high in rats (64%) and considerably lower in monkeys and dogs (30 and 38%, respectively). In rats and dogs, the major metabolic pathway of compound was S-oxidation, while in monkeys it was mainly metabolized via desglycolylation.

SOURCE – Pharmacia.

REFERENCES

1. Hester, J.B. Jr. et al. (Pharmacia Corp.) *Oxazolidinone antibacterial agents having a thiocarbonyl functionality*. EP 0984947, US 6218413, WO 9854161.

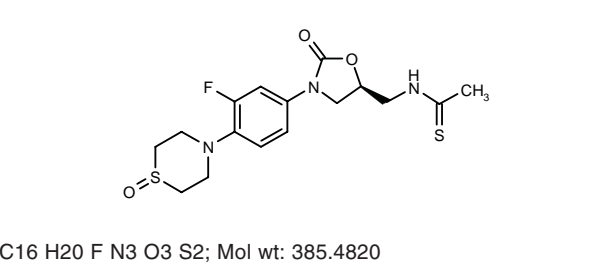
2. Friis, J.M. et al. *Interspecies comparison of the pharmacokinetics and metabolism of an oxazolidinone thiomide antibacterial (PNU-173995)*. 41st Intersci Conf Antimicrob Agents Chemother (Dec 16-19, Chicago) 2001, Abst F-1039a.

*Identified compound **272072** (see **272068**) Drug Data Rep 1999, 021(02): 0155.

PNU-177553

313029

N-[3-[3-Fluoro-4-(1-oxidothiophorolin-4-yl)phenyl]-2-oxooxazolidin-5(S)-ylmethyl]thioacetamide



ACTION – Oxazolidinone antibacterial with potent activity against common Gram-positive and Gram-negative bacteria including respiratory pathogens such as *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis* (MIC = 2-4 µg/ml), being at least 4-fold more active than linezolid against most of the organisms tested. Compound was also active against atypical respiratory pathogens such as *Mycoplasma pneumoniae* and *Chlamydia pneumoniae*, with MICs of 4.0-> 32.0 and 0.5-1.0 µg/ml, respectively. The antibacterial activity of compound was not affected by the presence of serum.

SOURCE – Pharmacia.

REFERENCES

1. Bohanon, M.J. (Pharmacia Corp.) *Enhancement of oxazolidinone antibacterial agents activity by using arginine derivs*. WO 9959616.

2. Hester, J.B. Jr. et al. (Pharmacia Corp.) *Oxazolidinone antibacterial agents having a thiocarbonyl functionality*. EP 0984947, US 6218413, WO 9854161.

3. Hester, J.B. Jr. et al. (Pharmacia Corp.) *Oxazolidinone antibacterial agents having a thiocarbonyl functionality*. EP 1133493, WO 0032599.

4. Mesfin, G.-M. and Jensen, R.K. (Pharmacia Corp.) *Use of thioamide oxazolidinones for the treatment of bone resorption and osteoporosis*. WO 0180841.

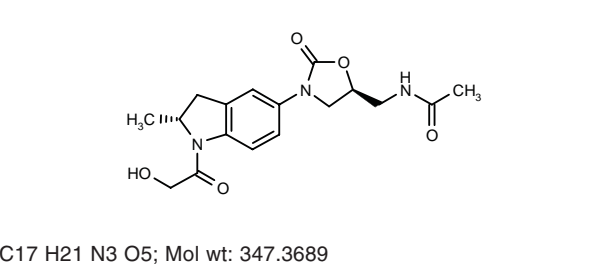
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6. Watts, J.L. et al. *In vitro activity of PNU-177553 against atypical respiratory pathogens*. 41st Intersci Conf Antimicrob Agents Chemother (Dec 16-19, Chicago) 2001, Abst F-1041.

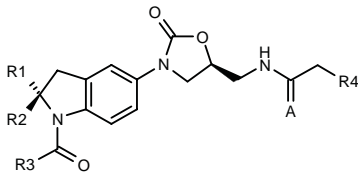
PNU-180164

313017

N-[3-[1-(2-Hydroxyacetyl)-2(R)-methyl-2,3-dihydro-1H-indol-5-yl]-2-oxooxazolidin-5(S)-ylmethyl]acetamide



ACTION – Oxazolidinone antibacterial active against methicillin-susceptible and -resistant *Staphylococcus aureus*, methicillin-resistant *Staphylococcus epidermidis*, *Streptococcus pneumoniae* and *Enterococcus faecalis* (MICs < 0.5-4 µg/ml), as well as against β-lactamase-positive strains of *Haemophilus influenzae* (MIC = 2-64 µg/ml) and *Moraxella catarrhalis* (MIC = 1-16 µg/ml). Compound exhibited good oral activity against systemic infections in mice caused by *S. aureus* (ED₅₀ = 1.8 mg/kg), with comparable activity to oral linezolid (ED₅₀ = 2.5 mg/kg) and s.c. vancomycin (ED₅₀ = 3.9 mg/kg). Other related compounds are:



Compound	R1	R2	R3	R4	A	Formula
PNU-184401* [298211]	Me	H	H	H	S	C ₁₆ H ₁₉ N ₃ O ₃ S
PNU-184402** [298212]	Me	H	CH ₂ OH	H	S	C ₁₇ H ₂₁ N ₃ O ₄ S
PNU-187706 [313019]	Me	H	Me	H	O	C ₁₇ H ₂₁ N ₃ O ₄
PNU-181095 [313020]	Me	H	H	H	O	C ₁₆ H ₁₉ N ₃ O ₄
PNU-181096 [313022]	Me	H	H	Me	O	C ₁₇ H ₂₁ N ₃ O ₄
PNU-247053 [313023]	H	Me	H	H	S	C ₁₆ H ₁₉ N ₃ O ₃ S

SOURCE – Pharmacia.

REFERENCES

1. Genin, M.J. et al. (Pharmacia Corp.) *Bicyclic oxazolidinones as antibacterial agent*. WO 0073301.

2. Barbachyn, M.R. et al. *The potentiating effect of remote chirality on the antibacterial activity of a series of 2-substituted indolyl phenyloxazolidinones*. 41st Intersci Conf Antimicrob Agents Chemother (Dec 16-19, Chicago) 2001, Abst F-1042.

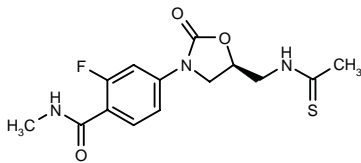
*Identified compound **298211** (see **298210**) Drug Data Rep 2001, 023(05): 0474.

Identified compound **298212 (see **298210**) Drug Data Rep 2001, 023(05): 0474.

VRC-3783

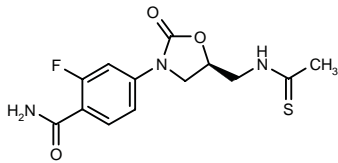
312985

4-5(*S*)-[(Ethanethioylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl]-2-fluoro-*N*-methylbenzamide



C14 H16 F N3 O3 S; Mol wt: 325.3624

ACTION – Phenyloxazolidinone thioamide antibacterial agent with excellent potency against *Staphylococcus aureus* (MIC = 1-2 µg/ml), *Staphylococcus epidermidis* (MIC = 0.5-1 µg/ml), vancomycin-resistant *Enterococcus faecium* (MIC = 2 µg/ml), *Moraxella catarrhalis* (MIC = 2-4 µg/ml) and *Streptococcus pneumoniae* (MIC = 1 µg/ml). Compound exhibited a good pharmacokinetic profile in rats, with high oral bioavailability (75-99%) and acceptable systemic clearance (13.5 ml/min). In a multidrug-resistant *S. aureus* septicemia model in mice, compound showed comparable efficacy to linezolid, with respective ED₅₀ values of 6.2 and 5.6 mg/kg p.o. Another related compound is:



VRC-4104 [312986]: C13 H14 F N3 O3 S

SOURCES – Pharmacia; Versicor.

REFERENCES

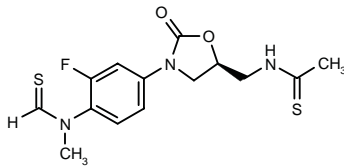
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2. Gordeev, M.F. et al. *4'-Amido phenyloxazolidinone thioamides: Antimicrobial activity and pharmacokinetics in rat*. 41st Intersci Conf Antimicrob Agents Chemother (Dec 16-19, Chicago) 2001, Abst F-1047.

VRC-3807

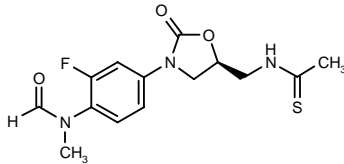
312983

N-[3-[3-Fluoro-4-[*N*-methyl-*N*-(thioformyl)amino]phenyl]-2-oxooxazolidin-5(*S*)-ylmethyl]thioacetamide



C14 H16 F N3 O2 S2; Mol wt: 341.4294

ACTION – Oxazolidinone antibacterial agent with exceptional potency against Gram-positive and Gram-negative bacteria including *Staphylococcus aureus* (MIC = 0.25-0.5 µg/ml), *Staphylococcus epidermidis* (MIC = 0.13 µg/ml), *Streptococcus pneumoniae* (MIC = 0.12 µg/ml) and vancomycin-resistant *Enterococcus faecium* (MIC = 0.5 µg/ml). Compound was also active against *Haemophilus influenzae* and *Moraxella catarrhalis* (MIC = 1-4 µg/ml). Another related compound is:



VRC-3808 [312984]: C14 H16 F N3 O3 S

SOURCES – Pharmacia; Versicor.

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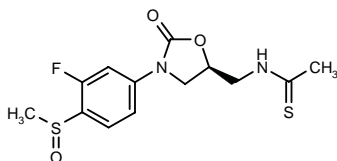
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VRC-3909

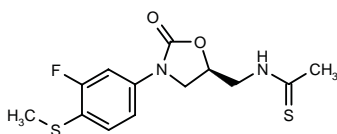
312982

N-[3-[3-Fluoro-4-(methylsulfinyl)phenyl]-2-oxooxazolidin-5(S)-ylmethyl]thioacetamide



C13 H15 F N2 O3 S2; Mol wt: 330.4025

ACTION – Oxazolidinone antibacterial agent active against Gram-positive and Gram-negative bacteria including *Staphylococcus aureus*, *Staphylococcus epidermidis*, vancomycin-resistant *Enterococcus faecium* and *Streptococcus pneumoniae* (MIC = 0.25-2 µg/ml), *Haemophilus influenzae* and *Moraxella catarrhalis* (MIC = 4-8 µg/ml). Another related compound is:



VRC-3803 [312981]: C13 H15 F N2 O2 S2

SOURCES – Pharmacia; Versicor.

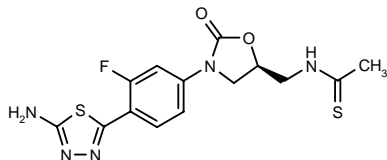
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VRC-3923

312987

N-[3-[4-(5-Amino-1,3,4-thiadiazol-2-yl)-3-fluorophenyl]-2-oxooxazolidin-5(S)-ylmethyl]thioacetamide



C14 H14 F N5 O2 S2; Mol wt: 367.4276

ACTION – Phenylloxazolidinone antibacterial agent active against Gram-positive and fastidious Gram-negative bacteria including *Staphylococcus aureus*, *Staphylococcus epidermidis*, vancomycin-resistant *Enterococcus faecium*, *Streptococcus pneumoniae* and *Moraxella catarrhalis* (MIC = 0.13-1 µg/ml). Compound was also active against *Haemophilus influenzae* (MIC = 4-16 µg/ml).

SOURCES – Pharmacia; Versicor.

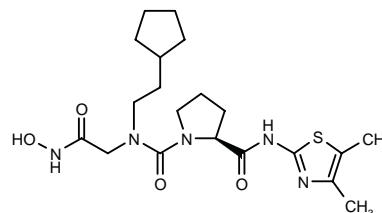
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VRC-4307

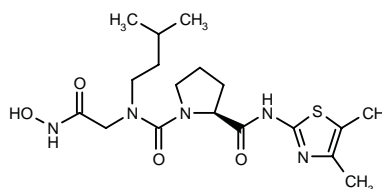
307001

N¹-(2-Cyclopentylethyl)-N²-(4,5-dimethylthiazol-2-yl)-N¹-(N-hydroxycarbamoylmethyl)pyrrolidine-1,2(S)-dicarboxamide



C20 H31 N5 O4 S; Mol wt: 437.5619

ACTION – Antibacterial agent, a selective inhibitor of the bacterial metalloprotease peptide deformylase (IC₅₀ = 2 and 8 nM against enzyme from *Escherichia coli* and *Streptococcus pneumoniae*, respectively) active against *Staphylococcus aureus*, *S. pneumoniae*, *Moraxella catarrhalis* and *Haemophilus influenzae* (MIC = 0.1-4 µg/ml). Further *in vitro* examination revealed bactericidal activity against *H. influenzae* and a low frequency of resistance. *In vivo*, parenteral doses of compound protected mice from septicemia caused by *S. aureus* Smith (ED = 30.8 mg/kg s.c.), but it was poorly active when given orally. Pharmacokinetic experiments showed that it was rapidly cleared from mouse serum (t_{1/2} = 0.1 h) and was not orally bioavailable. Moreover, it was rapidly metabolized *in vitro* by rat liver microsomes, although it was much more stable in human liver microsomes. Another related compound is:



VRC-4232 [EN:307002]: C18 H29 N5 O4 S

SOURCES – Novartis; Versicor.

REFERENCES

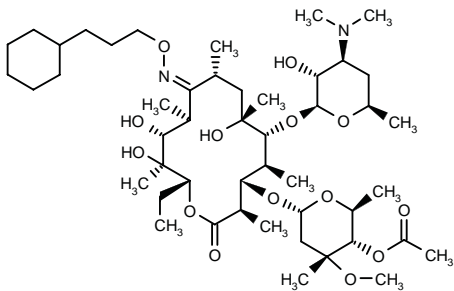
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4. Lewis, J.G. et al. *Iterative parallel synthesis-derived N-alkyl urea hydroxamic acids: A new class of peptide deformylase inhibitors*. 41st Intersci Conf Antimicrob Agents Chemother (Dec 16-19, Chicago) 2001, Abst F-358.

ANTIMYCOBACTERIAL AGENTS

GI-448

312524

4''-O-Acetylerythromycin A 9-[O-(3-cyclohexylpropyl)-oxime]



C48 H86 N2 O14; Mol wt: 915.2074

ACTION– Macrolide antibiotic, an erythromycin derivative active against both clarithromycin-susceptible and -resistant *Mycobacterium avium* complex (MAC) strains (MIC = 1.56 and 3.13 µg/ml, respectively, vs. 1.56 and > 50 µg/ml, respectively, for clarithromycin). Compound was also active against *Mycobacterium intracellulare* (MIC = 0.78-1.56 µg/ml), as well as multidrug-resistant *Mycobacterium tuberculosis* (MIC = 1.56-3.13 µg/ml), but it was inactive against a panel of Gram-positive and Gram-negative bacteria. In a model of disseminated infection induced in mice by clarithromycin-susceptible MAC, compound (12.5-50 mg/kg p.o.) reduced spleen bacterial counts in a dose-dependent manner and was more effective than clarithromycin; when the infections were caused by clarithromycin-resistant MAC strains, compound (50-100 mg/kg p.o.) retained good activity whereas clarithromycin was inactive.

SOURCE – Hokuriku.

REFERENCES

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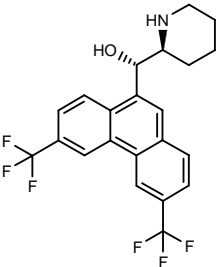
2. Takahashi, Y. et al. *Anti-Mycobacterium avium-complex activity of GI-448, a novel macrolide.* 41st Intersci Conf Antimicrob Agents Chemother (Dec 16-19, Chicago) 2001, Abst F-1175.

3. Yoshida, T. et al. *Discovery and SAR of macrolide agents with potent activities against Mycobacterium avium-complex.* 41st Intersci Conf Antimicrob Agents Chemother (Dec 16-19, Chicago) 2001, Abst F-1176.

RTI-1170-1-1

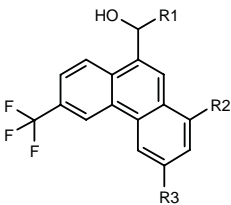
313598

(+)-*threo*-1-[3,6-Bis(trifluoromethyl)phenanthren-9-yl]-1-(2-piperidinyl)methanol



C22 H19 F6 N O; Mol wt: 427.3861

ACTION – Antimycobacterial agent, a phenanthrene analogue in which the bistrifluoromethylquinoline moiety of mefloquine is replaced by a bistrifluoromethylphenanthrene; it shows 4-16-fold higher potency than the parent compound against *Mycobacterium avium* including clarithromycin-resistant strains (MIC₅₀ = 2 µg/ml). Other related compounds are:



Compound	R1	R2	R3	Isomer	Formula
RTI-1164-1-1 [313595]	2-Pip	H	CF3	(-)-erythro	C ₂₂ H ₁₉ F ₆ NO
RTI-1165-2-1 [313596]	2-Pip	H	CF3	(+)-erythro	C ₂₂ H ₁₉ F ₆ NO
RTI-1171-1-2 [313597]	2-Pip	H	CF3	(-)-threo	C ₂₂ H ₁₉ F ₆ NO
RTI-1160-2-1 [313599]	CH2N(Bu)2	Cl	Cl	(-)-R	C ₂₅ H ₂₈ Cl ₂ F ₃ NO
RTI-1159-2-1 [313600]	CH2N(Bu)2	Cl	Cl	(+)-S	C ₂₅ H ₂₈ Cl ₂ F ₃ NO

SOURCE – Research Triangle Institute, Research Triangle Park, NC (US).

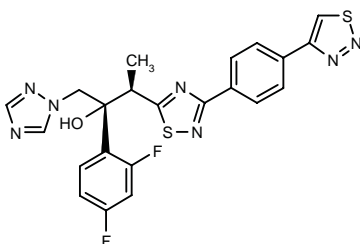
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ANTIFUNGAL AGENTS

312179

2-(*R*)-(2,4-Fluorophenyl)-3-(*R*)-[3-[4-(1,2,3-thiadiazol-4-yl)phenyl]-1,2,4-thiadiazol-5-yl]-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol



C22 H17 F2 N7 O S2; Mol wt: 497.5523

ACTION – Antifungal agent with *in vitro* activity against *Candida albicans* CY1002 ($IC_{80} = 0.00093 \mu\text{g/ml}$), *Aspergillus fumigatus* 437 ($IC_{80} = 0.11 \mu\text{g/ml}$), *Rhizopus oryzae* CFF1118 ($IC_{80} = 0.0023 \mu\text{g/ml}$) and *Absidia corymbifera* CF1001 ($IC_{80} = 0.0057 \mu\text{g/ml}$).

SOURCE – Basilea Pharmaceutica.

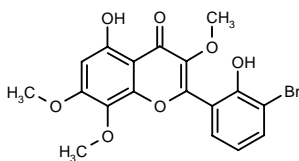
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CJ-19784

313838

2-(3-Bromo-2-hydroxyphenyl)-5-hydroxy-3,7,8-trimethoxy-4*H*-1-benzopyran-4-one



C18 H15 Br O7; Mol wt: 423.2135

ACTION – Antifungal agent active against *Candida albicans* and *Aspergillus fumigatus* ($IC_{50} = 0.11$ and $0.54 \mu\text{g/ml}$, respectively) with low cytotoxicity against HeLa cells ($IC_{50} = 81 \mu\text{g/ml}$).

SOURCE – Pfizer.

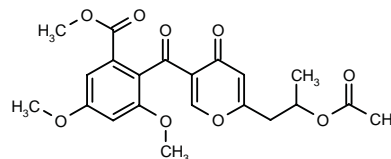
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FKI-0076

310268

2-[6-(2-Acetoxypropyl)-4-oxo-4*H*-pyran-3-ylcarbonyl]-3,5-dimethoxybenzoic acid methyl ester



C21 H22 O9; Mol wt: 418.3958

ACTION – Compound isolated from *Talaromyces flavus* strain FKI-0076 (FERM BP-7037), found to potentiate the activity of azole-type antifungal agents, and therefore considered to have potential for overcoming fungal drug resistance. While devoid of antibacterial and antifungal activity, in combination with miconazole title compound inhibited the growth of *Candida albicans* KF1 and *Saccharomyces cerevisiae* KF26.

SOURCE – Kitasato Institute, Tokyo (JP).

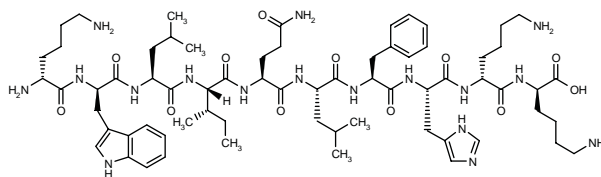
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XMP-620

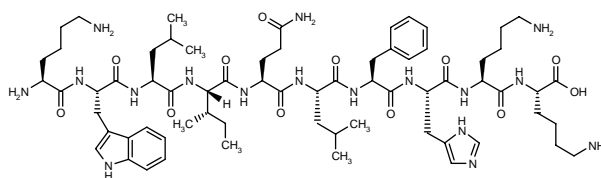
313168

D-Lysyl-D-tryptophyl-L-leucyl-L-isoleucyl-L-glutaminy-L-leucyl-L-phenylalanyl-L-histidyl-D-lysyl-D-lysine



C67 H105 N17 O12; Mol wt: 1340.6730

ACTION – Antifungal peptide derived from domain III of bactericidal/permeability-increasing protein (BPI), with moderate *in vitro* activity against *Candida albicans* (MIC = $4 \mu\text{g/ml}$), *Aspergillus fumigatus* (MIC = $16.0 \mu\text{g/ml}$), *Cryptococcus neoformans* (MIC = $0.125 \mu\text{g/ml}$) and *Trichophyton mentagrophytes* (MIC = $1.0 \mu\text{g/ml}$). Compound exhibited good serum stability and excellent efficacy in a murine model of candidiasis, where the dose of 10 mg/kg i.v. produced significant protection against mortality (80% survival at 28 days). Another related compound is:



XMP-293 [313167]: C67 H105 N17 O12

SOURCE – Xoma.

REFERENCES

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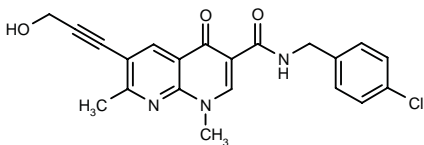
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ANTIVIRAL DRUGS

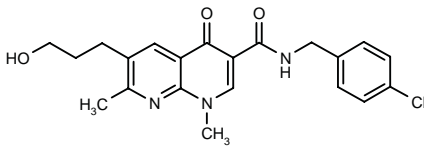
311861

N-(4-Chlorobenzyl)-6-(3-hydroxy-1-propynyl)-1,7-dimethyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxamide



C21 H18 Cl N3 O3; Mol wt: 395.8442

ACTION – Antiviral agent, particularly useful for the treatment of infections caused by herpes simplex virus (HSV), varicella-zoster virus (VZV), Epstein-Barr virus and human cytomegalovirus (HCMV). Compound gave IC₅₀ values of 1.8, 1.9 and 1.1 μM, respectively, against polymerases of HCMV, HSV and VZV. Another exemplified 4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxamide is:



311862: C21 H22 Cl N3 O3

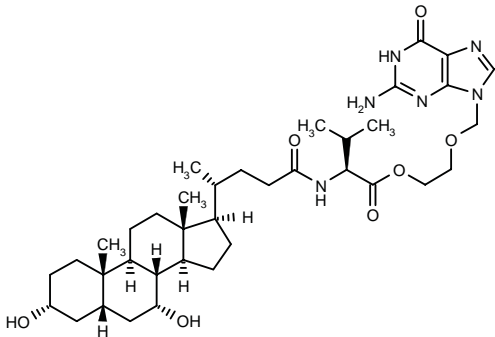
SOURCE – Pharmacia.

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1. Vaillancourt, V.A. and Thorarensen, A. (Pharmacia Corp.) *4-Oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxamides as antiviral agents.* WO 0174816.

311994

N-[(3α,5β,7α)-3,7-Dihydroxy-24-oxocholan-24-yl]-L-valine 2-(guanin-9-ylmethoxy)ethyl ester



C37 H58 N6 O7; Mol wt: 698.9002

ACTION – Bile acid-containing aciclovir prodrug that is reported to be effective for increasing the bioavailability and intestinal permeability of the active compound.

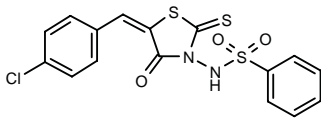
SOURCE – University of Maryland, Baltimore, MD (US).

REFERENCES

1. Polli, J.E. et al. (University of Maryland) *Bile acid containing prodrugs with enhanced bioavailability.* WO 0176531.

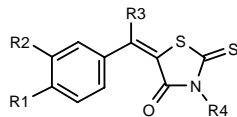
312077

N-[5-(4-Chlorobenzylidene)-4-oxo-2-thioxothiazolidin-3-yl]benzenesulfonamide

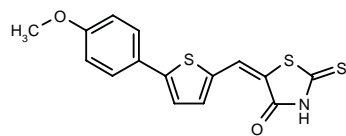


C16 H11 Cl N2 O3 S3; Mol wt: 410.9249

ACTION – Antiviral agent, an inhibitor of hepatitis C virus (HCV) NS5B polymerase (IC₅₀ = 30 μM or less), useful for the treatment of HCV infection. Other exemplified compounds include the following:



Compound	R1	R2	R3	R4	Formula
312078	H	Cl	H	NHSO2Ph	C ₁₆ H ₁₁ ClN ₂ O ₃ S ₃
312079	Cl	Cl	Me	NHSO2Ph	C ₁₇ H ₁₂ Cl ₂ N ₂ O ₃ S ₃
312080	H	CN	H	NHSO2Ph	C ₁₇ H ₁₁ N ₃ O ₃ S ₃
312081	Cl	Cl	H	2,5-(Me)2-PhSO2NH	C ₁₈ H ₁₄ Cl ₂ N ₂ O ₃ S ₃
312082	Cl	Cl	H	3-NO2-PhSO2NH	C ₁₆ H ₉ Cl ₂ N ₃ O ₃ S ₃
312083	NO2	H	H	NH2	C ₁₀ H ₇ N ₃ O ₃ S ₂
312084	NO2	H	H	H	C ₁₀ H ₆ N ₂ O ₃ S ₂



312085: C15 H11 N O2 S3

SOURCE – Tularik.

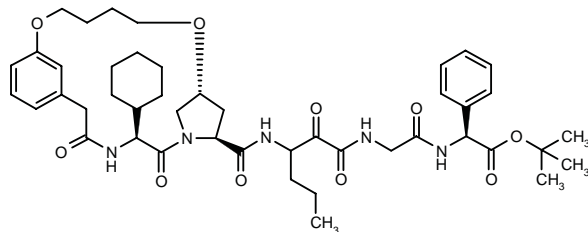
REFERENCES

1. Jaen, J.C. et al. (Tularik Inc.) *NS5B HCV polymerase inhibitors*. WO 0177091.

312095

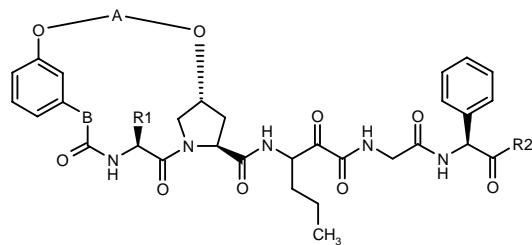
N-[2-[3-(4-Hydroxybutoxy)phenyl]acetyl]-L-cyclohexylglycyl-4(*R*)-hydroxy-L-prolyl-DL-3-amino-2-oxohexanoyl-glycyl-L-phenylglycine *tert*-butyl ester cyclic ether

2(*S*)-[*N*-[3-[(5*S*,8*S*,10*R*)-5-Cyclohexyl-3,6-dioxo-11,16-dioxo-4,7-diazatricyclo[15.3.1.1^{7,10}]docosa-1(21),17,19-trien-8-ylcarboxamido]-2-oxohexanoyl]-glycylamino]-2-phenylacetic acid *tert*-butyl ester

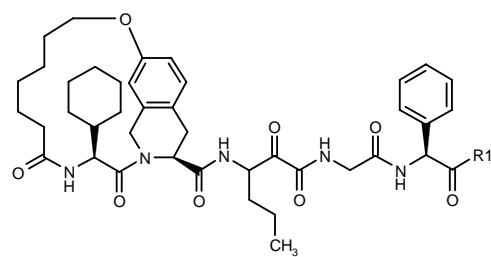


C45 H61 N5 O10; Mol wt: 832.0019

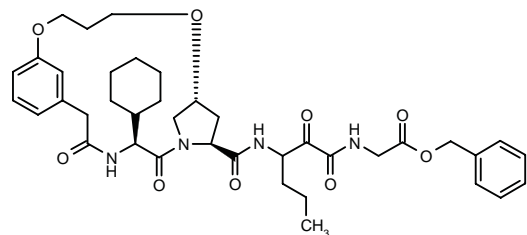
ACTION – Antiviral agent, an inhibitor of hepatitis C virus (HCV) NS3 serine protease ($K_i < 100$ nM). Other exemplified macrocyclic compounds are:



Compound	R1	R2	A	B	Isomer	Formula
312097	cyclohexyl	N(Me)2	-(CH2)3-	-CH2-	S	C ₄₂ H ₅₆ N ₆ O ₉
312098	cyclohexyl	t-BuO	-(CH2)3-	-CH2-		C ₄₄ H ₅₉ N ₅ O ₁₀
312099	cyclohexyl	N(Me)2	-(CH2)4-	-CH2-	R	C ₄₃ H ₅₈ N ₆ O ₉
312100	cyclohexyl	N(Me)2	-(CH2)4-	-CH2-	S	C ₄₃ H ₅₈ N ₆ O ₉
312101	cyclohexyl	N(Me)2	-(CH2)2-	-CH2-	S	C ₄₁ H ₅₄ N ₆ O ₉
312102	cyclohexyl	t-BuO	-(CH2)2-	-CH2-		C ₄₃ H ₅₇ N ₅ O ₁₀
312103	t-Bu	N(Me)2	-(CH2)3-	-CH2-	S	C ₄₀ H ₅₄ N ₆ O ₉
312104	cyclohexyl	t-BuO	-(CH2)2-	-(CH2)2-		C ₄₄ H ₅₉ N ₅ O ₁₀
312106	cyclohexyl	N(Me)2	-CH2CH2-C(Me)2-	-CH2-		C ₄₄ H ₆₀ N ₆ O ₉



Compound	R1	Isomer	Formula
312107	N(Me)2	S	C ₄₃ H ₅₈ N ₆ O ₈
312108	t-BuO		C ₄₅ H ₆₁ N ₅ O ₉



312105: C39 H50 N4 O9

SOURCE – Schering-Plough.

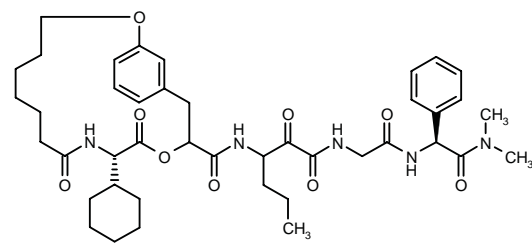
REFERENCES

1. Chen, K.X. et al. (Schering Corp.) *Macrocyclic NS3-serine protease inhibitors of hepatitis C virus comprising N-cyclic 2 moieties*. WO 0177113.

312353

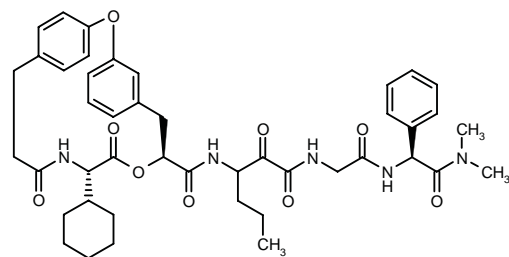
11(*S*)-Cyclohexyl-*N*-[1-[2-[*N*-[1(*S*)-(*N,N*-dimethylcarbamoyl)-1-phenylmethyl]carbamoylmethylamino]-oxalyl]butyl]-9,12-dioxo-2,13-dioxo-10-azabicyclo[14.3.1]icosa-1(20),16,18-triene-14-carboxamide

N-[3-[11(*S*)-Cyclohexyl-9,12-dioxo-2,13-dioxo-10-azabicyclo[14.3.1]icosa-1(20),16,18-trien-14-ylcarboxamido]-2-oxohexanoyl]-glycyl-L-phenylglycine *N,N*-dimethylamide



C42 H57 N5 O9; Mol wt: 775.9383

ACTION – Macrocyclic compound that acts as a hepatitis C virus (HCV) NS3 serine protease inhibitor ($EC_{50} = 9$ μ M). Potentially useful for the treatment of HCV infection. Another exemplified compound is:



312354: C44 H53 N5 O9

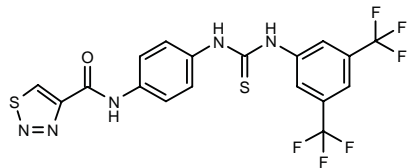
SOURCE – Schering-Plough.

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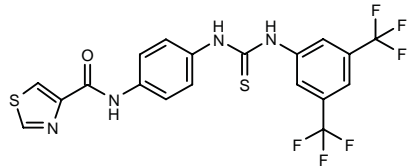
312705

N-[4-[3-[3,5-Bis(trifluoromethyl)phenyl]thioureido]phenyl]-1,2,3-thiadiazole-4-carboxamide



C18 H11 F6 N5 O S2; Mol wt: 491.4389

ACTION – Antiviral agent, a thiourea derivative active against human cytomegalovirus (HCMV; IC₅₀ = 37 nM) and selective against other viruses including herpes simplex virus type 1 (HSV-1), varicella-zoster virus, respiratory syncytial virus, as well as murine and rhesus cytomegalovirus (IC₅₀ > 20 μM). Compound possesses a unique mechanism of action, inhibiting gB-mediated viral fusion, and was also active against clinical isolates of HCMV with resistance to ganciclovir, foscarnet or cidofovir (IC₅₀ = 0.022-1.456 μM). Compound exhibited a favorable pharmacokinetic profile in mice, rats, dogs and monkeys. Another related compound is:



[312707]: C19 H12 F6 N4 O S2

SOURCE – Wyeth Pharmaceuticals.

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1. Bloom, J.D. et al. (American Home Products Corporation) *α-Methylbenzyl-containing thiourea inhibitors of herpes viruses containing a phenylenediamine group*. WO 0034260.

2. Bloom, J.D. et al. (American Home Products Corporation) *Heterocyclic carboxamide-containing thiourea inhibitors of herpes viruses containing a subst. phenylenediamine group*. US 6166028, WO 0034261.

3. Bloom, J.D. et al. (American Home Products Corporation) *Heterocyclic carboxamide-containing thiourea inhibitors of herpes viruses containing phenylenediamine group*. WO 0034258.

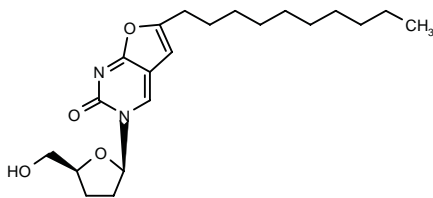
4. Bloom, J.D. et al. (American Home Products Corporation) *Thiourea inhibitors of herpes viruses*. EP 1137632, WO 0034238.

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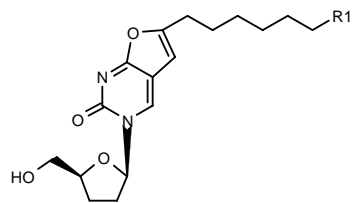
312861

6-Decyl-3-(2',3'-dideoxy-β-D-ribofuranosyl)furo[2,3-*d'*]pyrimidin-2(3*H*)-one



C21 H32 N2 O4; Mol wt: 376.4938

ACTION – Antiviral pyrimidine nucleoside analogue particularly active against cytomegalovirus (CMV). The compound showed anti-CMV activity comparable to that of ganciclovir and an acceptable toxicity level. Other exemplified compounds are:



Compound	R1	Formula
312862	H	C ₁₇ H ₂₄ N ₂ O ₄
312863	Et	C ₁₉ H ₂₈ N ₂ O ₄
312864	C6H13	C ₂₃ H ₃₆ N ₂ O ₄
312866	C8H17	C ₂₅ H ₄₀ N ₂ O ₄
312868	Pr	C ₂₀ H ₃₀ N ₂ O ₄
312869	C5H11	C ₂₂ H ₃₄ N ₂ O ₄
312870	(CH2)3OBu	C ₂₄ H ₃₈ N ₂ O ₅
312873	(CH2)3O(CH2)4Cl	C ₂₄ H ₃₇ ClN ₂ O ₅

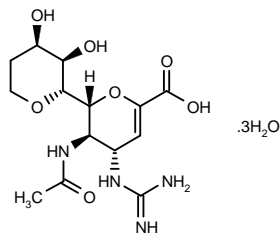
SOURCES – University College, Cardiff, Cardiff (GB); Rega Institute for Medical Research, Leuven (BE).

REFERENCES

1. McGuigan, C. et al. (Rega Institute for Medical Research;University College, Cardiff) *Anti-viral pyrimidine nucleoside analogues*. WO 0185749.

313215

5-Acetamido-4-guanidino-2,6:7,11-dianhydro-3,4,5,10-tetradexy-D-erythro-D-galacto-undec-2-enonic acid trihydrate



C14 H22 N4 O7 . 3H2O; Mol wt: 412.3932

ACTION – A representative compound from a series of sialic acid derivatives with efficacy against influenza virus; it afforded a 62.5% survival rate in mice infected with the A/PR/8/34 influenza virus strain following p.o. administration at 5 mg/kg, while all untreated mice died.

SOURCE – Sankyo.

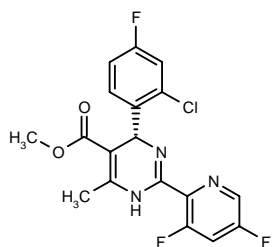
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BAY-41-4109*

295321

(–)-4(*R*)-(2-Chloro-4-fluorophenyl)-2-(3,5-difluoropyridin-2-yl)-6-methyl-1,4-dihydropyrimidine-5-carboxylic acid methyl ester



C18 H13 Cl F3 N3 O2; Mol wt: 395.7667

ACTION – Non-nucleoside inhibitor of human hepatitis B virus (IC_{50} = 53 nM for reduction of HBV DNA in human hepatoma HepG2.2.15 cells) with low cytotoxicity in uninfected cells (CC_{50} = 7 μ M). Compound inhibited both viral DNA and viral cores in HepG2.2.15 cells and HBV-transfected cell lines, whereas it did not affect the activity of endopolymerase and had no effect on other DNA or RNA viruses. *In vivo* in a transgenic mouse model, oral doses of 3-100 mg/kg b.i.d. or t.i.d. for up to 28 days dose-dependently decreased viral DNA in the liver and plasma with efficacy comparable to lamivudine. However, unlike lamivudine, compound reduced cytoplasmic HBV core antigen (HBcAg) in the liver of mice. Pharmacokinetic studies in mice showed rapid absorption, 30% bioavailability and dose-proportional plasma levels.

SOURCE – Bayer.

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6. Paessens, A. et al. *BAY 41-4109: A novel anti-HBV agent.* 41st Intersci Conf Antimicrob Agents Chemother (Dec 16-19, Chicago) 2001, Abst 12.
7. Paessens, A. et al. *BAY 41-4109: A novel non-nucleosidic and highly potent inhibitor of human hepatitis B virus (HBV). Part 2: In vitro profile.* 41st Intersci Conf Antimicrob Agents Chemother (Dec 16-19, Chicago) 2001, Abst F-1665.

8. Weber, O. et al. *BAY 41-4109: A novel non-nucleosidic and highly potent inhibitor of human hepatitis B virus. Part 3: In vitro profile.* 41st Intersci Conf Antimicrob Agents Chemother (Dec 16-19, Chicago) 2001, Abst F-1666.

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*Identified compound **295321** Drug Data Rep 2001, 023(03): 0280.

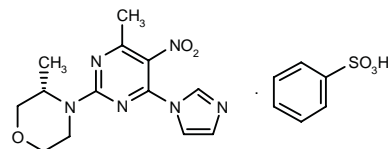
T-0902611

292272

4-[4-(1*H*-Imidazol-1-yl)-6-methyl-5-nitropyrimidin-2-yl]-3(*S*)-methylmorpholine benzenesulfonate

T-611

T-902611



C13 H16 N6 O3 . C6 H6 O3 S; Mol wt: 462.4848

ACTION – Non-nucleoside inhibitor of human cytomegalovirus (HCMV; IC_{50} = 70 nM for inhibition of viral replication) with superior activity to ganciclovir and cidofovir (IC_{50} = 1 and 0.35 μ M, respectively) and low cytotoxicity in Jurkat cells (CC_{50} = 50 μ M). Compound exhibited a favorable oral pharmacokinetic profile in rats and dogs and low toxicity in rats after 14 days of oral administration. Currently undergoing phase II trials in AIDS patients with HCMV infection.

SOURCE – Tularik.

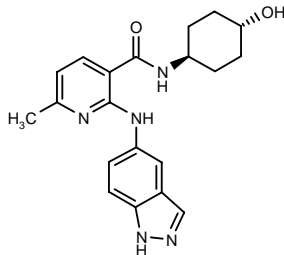
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1. Powers, J.P. (Tularik Inc.) *Arylsulfonic acid salts of pyrimidine-based antiviral agents.* WO 0151485.
2. Buchanan, J. et al. *Phase I multiple dose study for pharmacokinetics, safety and tolerability of T0902611, a novel investigational anti-cytomegalovirus agent.* 39th Annu Meet Infect Dis Soc Am (Oct 25-28, San Francisco) 2001, Abst 460.
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6. Wright, M. et al. *Preclinical pharmacokinetics and metabolism of T0902611, a novel inhibitor of human cytomegalovirus.* 39th Annu Meet Infect Dis Soc Am (Oct 25-28, San Francisco) 2001, Abst 458.
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AIDS MEDICINES

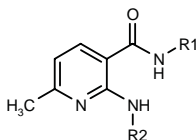
312186

trans-*N*-(4-Hydroxycyclohexyl)-2-(1 *H*-indazol-5-ylamino)-6-methylpyridine-3-carboxamide



C20 H23 N5 O2; Mol wt: 365.4347

ACTION – Antiviral agent that acts as a reverse transcriptase (RT) inhibitor and is particularly useful for the treatment of hepatitis B and C virus (HBV, HCV) and HIV infections. This compound inhibited HBV RT, HCV RT and HIV RT by 80, 90 and 80%, respectively, at 1 µg/ml. It displayed low cytotoxicity against HepG2 cells, and gave an LD₅₀ value > 2 g/kg when administered orally to rats. Other 6-methylnicotinamide derivatives include the following:



Compound	R1	R2	Formula
312187	4-morpholinyl	5-indazolyl	C ₁₈ H ₂₀ N ₆ O ₂
312189	2-Pyr-CH ₂ CH ₂	5-indazolyl	C ₂₁ H ₂₀ N ₆ O
312204	CH ₂ CH ₂ N(Me) ₂	6-indazolyl	C ₁₈ H ₂₂ N ₆ O
312205	1-imidazolyl-(CH ₂) ₃	6-indazolyl	C ₂₀ H ₂₁ N ₇ O
312206	2-Pyr-NH	6-indazolyl	C ₁₉ H ₁₇ N ₇ O

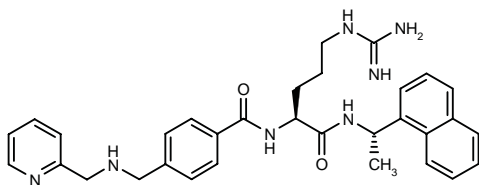
SOURCE – Dong-Wha.

REFERENCES

1. Yoon, S.-J. et al. (Dong-Wha Pharmaceuticals Industry Co. Ltd) *6-Methylnicotinamide derivs. as antiviral agents*. WO 0178648.

312804

*N*¹-[1 (*S*)-(1-Naphthyl)ethyl]-*N*²-[4-(pyridin-2-ylmethyl-aminomethyl)benzoyl]-L-argininamide



C32 H37 N7 O2; Mol wt: 551.6913

ACTION – Antiviral agent particularly useful for the treatment of AIDS. The compound was found to be active against HIV *in vitro* (EC₅₀ = 0.043 µM in HIV-1_{III_B}-infected MT-4 cells) and *in vivo* in SCID mice. No deaths were observed in mice 5 days after treatment at a dose of 50 mg/kg i.p. twice daily for 4 days.

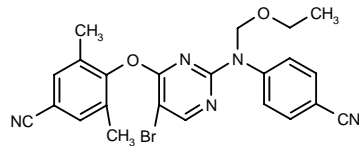
SOURCE – Kureha.

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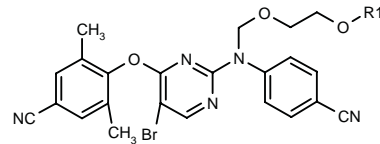
313089

4-[5-Bromo-2-[*N*-(4-cyanophenyl)-*N*-(ethoxymethyl)-amino]pyrimidin-4-yloxy]-3,5-dimethylbenzonitrile



C23 H20 Br N5 O2; Mol wt: 478.3480

ACTION – Prodrug of an anti-HIV agent with an IC₅₀ of 0.165 µM for inhibition of HIV-1-induced cytopathic effect in MT-4 cells following metabolic activation of the prodrug by treatment with human subcellular liver fraction. Other exemplified pyrimidines include the following:



Compound	R1	Formula
313090	H	C ₂₃ H ₂₀ BrN ₅ O ₃
313091	COPh	C ₃₀ H ₂₄ BrN ₅ O ₄

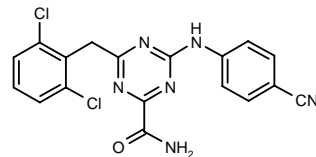
SOURCE – Janssen.

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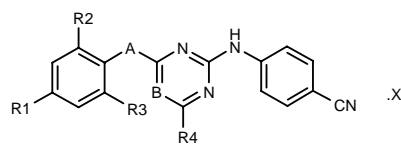
313094

4-(4-Cyanophenylamino)-6-(2,6-dichlorobenzyl)-1,3,5-triazine-2-carboxamide



C18 H12 Cl2 N6 O; Mol wt: 399.2398

ACTION – Anti-HIV agent with an IC₅₀ value of 0.165 µM for inhibition of HIV-1-induced cytopathic effect in MT-4 cells and a selectivity index of > 39,000. Other exemplified compounds are:



Compound	R1	R2=R3	R4	A	B	X	Formula
313095	H	Cl	3,5-dioxo-4-morpholinyl	-CH2-	N		C ₂₁ H ₁₄ Cl ₂ N ₆ O ₃
313096	H	Cl	4-OH-2-isoxazolidinyl	-CH2-	N	CF ₃ CO ₂ H	C ₂₀ H ₁₆ Cl ₂ N ₆ O ₂ .C ₂ HF ₃ O ₂
313098	CN	Me	CH ₂ OMe	-O-	C(Br)		C ₂₂ H ₁₈ BrN ₅ O ₂
313099	CN	Me	CH ₂ OH	-O-	C(Br)		C ₂₁ H ₁₆ BrN ₅ O ₂
313100	CN	Br	CH ₂ OH	-O-	C(Br)		C ₁₉ H ₁₀ Br ₃ N ₅ O ₂
313102	Me	Me	CONH ₂	-NH-	CH		C ₂₁ H ₂₀ N ₆ O
313103	Me	Me	CON(Me) ₂	-NH-	CH		C ₂₃ H ₂₄ N ₆ O
313105	Me	Me	CONH ₂	-NH-	C(Br)		C ₂₁ H ₁₈ BrN ₆ O

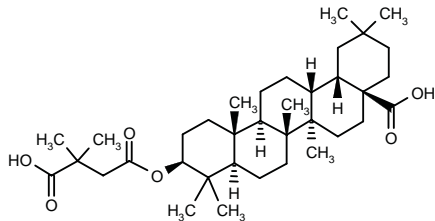
SOURCE – Janssen.

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1. Kukla, M.J. et al. (Janssen Pharmaceutica NV) HIV replication inhibitors. WO 0185700.

313153

3β-(3-Carboxy-3-methylbutyryloxy)oleanan-28-oic acid



C36 H58 O6; Mol wt: 586.8482

ACTION – Anti-HIV agent, an oleanolic acid derivative with high anti-HIV-1 activity (EC₅₀ = 0.0039 µg/ml) and low cytotoxicity (IC₅₀ = 13.7 µg/ml).

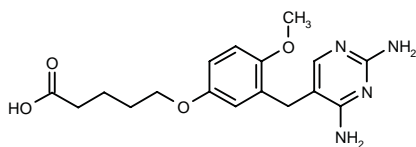
SOURCES – Biotech Research Laboratories; Chinese Academy of Sciences, Beijing (CN); University of North Carolina, Chapel Hill, NC (US).

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1. Zhu, Y.-M. et al. Synthesis and anti-HIV activity of oleanolic acid derivatives. Bioorg Med Chem Lett 2001, 11(24): 3115.

313258

5-[3-(2,4-Diaminopyrimidin-5-ylmethyl)-4-methoxyphenoxy]pentanoic acid



C17 H22 N4 O4; Mol wt: 346.3848

ACTION – Inhibitor of *Pneumocystis carinii* and *Mycobacterium avium* dihydrofolate reductase (IC₅₀ = 49 and 5.8 nM, respectively) with 80-660-fold selectivity over rat liver enzyme. Lead compound in the search for antifolates with potential clinical activity against *P. carinii* and other opportunistic infections in AIDS patients.

SOURCES – Harvard Medical School, Boston, MA (US); Indiana University, Indianapolis, IN (US).

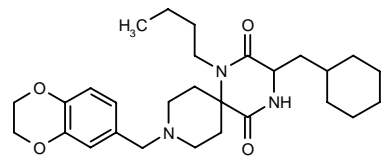
REFERENCES

1. Rosowsky, A. et al. Inhibition of *Pneumocystis carinii*, *Toxoplasma gondii*, and *Mycobacterium avium* dihydrofolate reductases by 2,4-diamino-5-[2-methoxy-5-(omega-carboxyalkyloxy)benzyl]pyrimidines: Marked improvement in potency relative to trimethoprim and species selectivity relative to piritrexim. J Med Chem 2002, 45(1): 233.

E-913

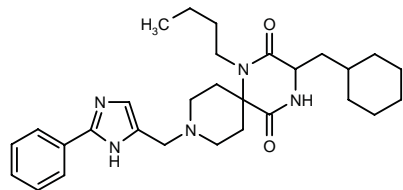
306336

1-Butyl-3-(cyclohexylmethyl)-9-(2,3-dihydro-1,4-benzodioxin-6-ylmethyl)-1,4,9-triazaspiro[5.5]undecane-2,5-dione



C28 H41 N3 O4; Mol wt: 483.6489

ACTION – Anti-HIV agent, a CCR5 antagonist (IC₅₀ = 2 nM) proven to specifically antagonize cellular Ca²⁺ mobilization induced by macrophage inflammatory protein-1α (MIP-1α; IC₅₀ = 20 nM). Compound strongly inhibited the replication of laboratory and primary R5 HIV-1 strains, as well as various multidrug-resistant monocyte/macrophage-tropic HIV-1 strains (IC₅₀ = 0.03-0.06 µM), and was inactive against T-cell-tropic (X4) HIV-1. However, when combined with the CXCR4 antagonist AMD-3100, compound synergistically inhibited the replication of dual-tropic HIV-1 and a 50:50 mixture of R5 and X4 HIV-1. No synergy or antagonism was seen when compound was administered in combination with zidovudine or nelfinavir. Another related compound is:



E-916 [306337]: C29 H41 N5 O2

SOURCE – Ono.

REFERENCES

1. Habashita, H. et al. (Ono Pharmaceutical Co., Ltd.) *Triazaspiro[5.5]undecane derivs. and drugs containing the same as the active ingredient*. WO 0140227.

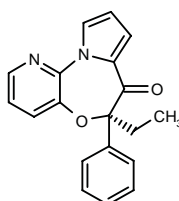
2. Maeda, K. et al. *Novel low molecular weight spirodiketopiperazine derivatives potentially inhibit R5 HIV-1 infection through their antagonistic effects on CCR5*. 9th Conf Retroviruses Opportunistic Infect (Feb 24-28, Seattle) 2002, Abst 400-T.

3. Maeda, K. et al. *Novel low molecular weight spirodiketopiperazine derivatives potentially inhibit R5 HIV-1 infection through their antagonistic effects on CCR5*. J Biol Chem 2001, 276(37): 35194.

(R)-(-)-PPO-464

314034

6(*R*)-Ethyl-6-phenylpyrido[3,2-*b*]pyrrolo[1,2-*d*][1,4]-oxazepin-7(6*H*)-one



C19 H16 N2 O2; Mol wt: 304.3474

ACTION – Anti-HIV-1 agent, the (*R*)-(-)-enantiomer of the non-nucleoside reverse transcriptase inhibitor (NNRTI) PPO-294 with good antiviral activity against wild-type HIV-1 and multidrug-resistant clinical isolates (EC_{50} = 0.04 and 3.4 μ M, respectively); significant synergistic antiviral activity was seen in combination with other RTIs such as nevirapine and zidovudine. In mice, compound exhibited a superior pharmacokinetic profile compared to the racemate; it readily crossed the blood–brain barrier following s.c. or p.o. administration and the plasma and brain C_{max} and AUC values were increased by concomitant administration of ritonavir.

SOURCES – Istituto di Ricerche Farmacologiche Mario Negri, Milano (IT); Sigma-Tau.

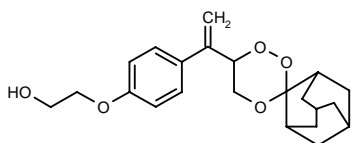
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1. Maga, G. et al. *The stereoselective targeting of a specific enzyme-substrate complex is the molecular mechanism for the synergic inhibition of HIV-1 reverse transcriptase by (R)-(-)-PPO464 - A novel generation of nonnucleoside inhibitors*. J Biol Chem 2001, 276(48): 44653.

TREATMENT OF PROTOZOAL DISEASES

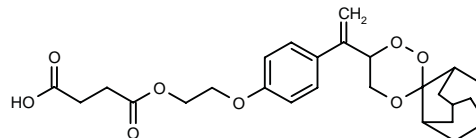
312405

2-[4-[1-(Spiro[adamantane-2,3'-[1,2,4]trioxan]-6'-yl)-vinyl]phenoxy]ethanol



C22 H28 O5; Mol wt: 372.4582

ACTION – Antimalarial agent reported to completely suppress parasitemia in various animal models of malaria following either i.m. or p.o. administration. Another exemplified substituted [1,2,4]trioxane derivative is:



312406: C26 H32 O8

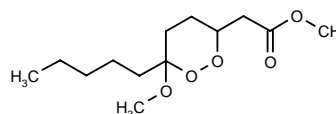
SOURCE – Council of Scientific and Industrial Research, New Delhi (IN).

REFERENCES

1. Singh, C. and Puri, S.K. (Council of Scientific and Industrial Research) *Substd. 1,2,4-trioxanes as antimalarial agents and a process of producing the substd. 1,2,4-trioxanes*. US 6316493.

314277

2-(6-Methoxy-6-pentyl-1,2-dioxan-3-yl)acetic acid methyl ester



C13 H24 O5; Mol wt: 260.3276

ACTION – Antimalarial agent with high *in vitro* activity against *Plasmodium falciparum* (IC_{50} = 0.12 μ M) and low cytotoxicity against KB 3-1 cells (IC_{50} = 43 μ M). Studies of the *in vivo* antimalarial activity of compound are in progress.

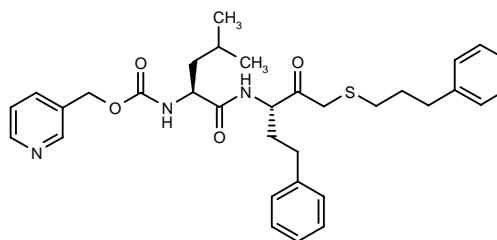
SOURCE – Osaka University, Osaka (JP).

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1. Murakami, N. et al. *New readily accessible peroxides with high anti-malarial potency*. Bioorg Med Chem Lett 2002, 12(1): 69.

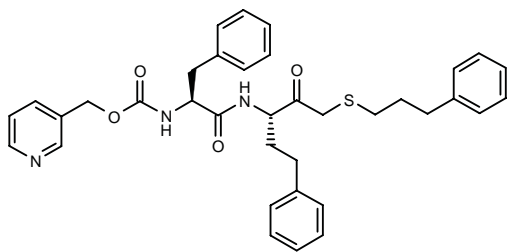
314645

*N*¹-[2-Oxo-1(*S*)-(2-phenylethyl)-3-(3-phenylpropylsulfany)propyl]-*N*²-(pyridin-3-ylmethoxycarbonyl)-*L*-leucinamide



C33 H41 N3 O4 S; Mol wt: 575.7699

ACTION – Antitrypanosomal agent, an inhibitor of the *Trypanosoma cruzi* cysteine protease cruzain (K_i = 1.1 nM) with high selectivity over other cysteine proteases including cathepsin B and cathepsin L (K_i = 1700 and 144.4 nM, respectively). Another related compound is:



314644: C36 H39 N3 O4 S

SOURCE – University of California, Berkeley, Berkeley CA (US).

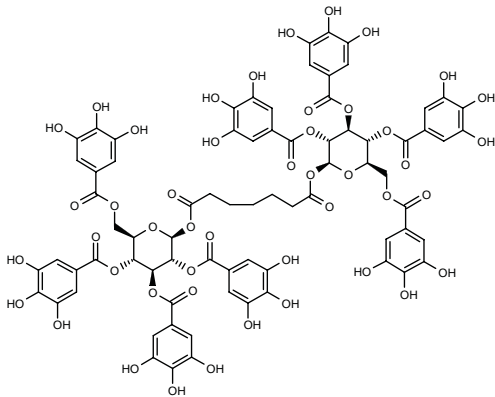
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1. Huang, L. et al. *Identification of potent and selective mechanism-based inhibitors of the cysteine protease cruzain using solid-phase parallel synthesis.* J Med Chem 2002, 45(3): 676.

TREATMENT OF SEPTIC SHOCK

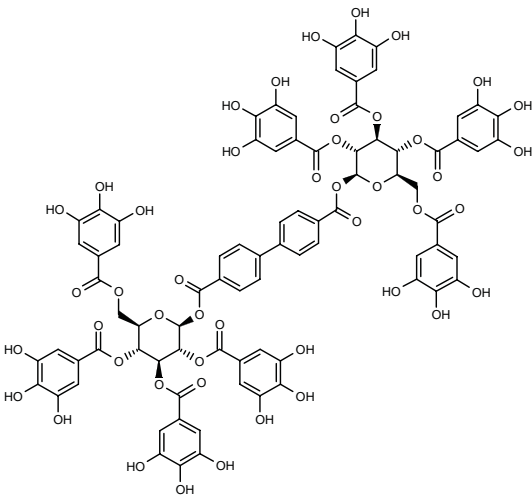
314330

1,1'-O-(1,7-Dioxoheptane-1,7-diyl)-bis[2,3,4,6-tetrakis-O-(3,4,5-trihydroxybenzoyl)-β-D-glucopyranose]



C75 H64 O46; Mol wt: 1701.2850

ACTION – Immunomodulator, a dimeric gallotannin analogue proven to inhibit endotoxin-induced TNF-α production from human peripheral blood mononuclear cells (30% inhibition at 5 μM). Comparable results were obtained *in vivo*, where a dose of 12.5 mg/kg by infusion decreased TNF-α levels by approximately 50%. Compound lacked IL-1β-stimulating activity both *in vitro* and *in vivo*. Potentially useful for the treatment of septic shock. Another related compound is:



314332: C82 H62 O46

SOURCE – Pennsylvania State University, Hershey, PA (US).

REFERENCES

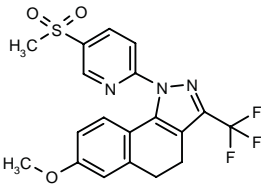
1. Feldman, K.S. (Penn State Research Foundation) *Gallotannins and ellagitannins as regulators of cytokine release.* WO 0136436.
2. Feldman, K.S. et al. *In vitro and in vivo inhibition of LPS-induced tumor necrosis factor-α production by dimeric gallotannin analogues.* Bioorg Med Chem 2002, 10(1): 47.

TREATMENT OF MUSCULOSKELETAL AND CONNECTIVE TISSUE DISEASES

ANTIARTHRITIC DRUGS

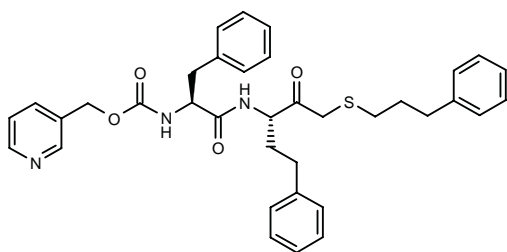
310615

7-Methoxy-1-[5-(methylsulfonyl)pyridin-2-yl]-3-(trifluoromethyl)-4,5-dihydro-1H-benzo[g]indazole



C19 H16 F3 N3 O3 S; Mol wt: 423.4134

ACTION – A selective cyclooxygenase type 2 (COX-2) inhibitor, considered to have potential in a broad range of inflammatory conditions including arthritis, fever, the common cold, dysmenorrhea, inflammatory bowel disease, Crohn's disease, emphysema, acute respiratory distress syndrome, asthma, bronchitis, chronic obstructive pulmonary disease, Alzheimer's disease, transplant rejection, cachexia, allergy, etc. Other specifically claimed pyrazole derivatives are:



314644: C36 H39 N3 O4 S

SOURCE – University of California, Berkeley, Berkeley CA (US).

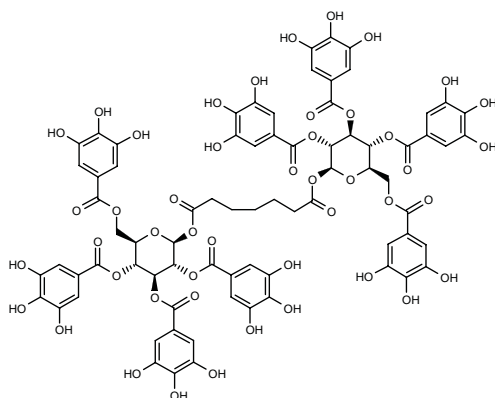
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TREATMENT OF SEPTIC SHOCK

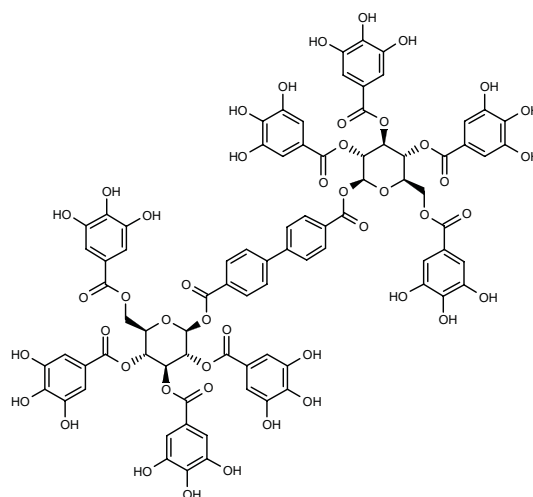
314330

1,1'-O-(1,7-Dioxoheptane-1,7-diyl)-bis[2,3,4,6-tetrakis-O-(3,4,5-trihydroxybenzoyl)-β-D-glucopyranose]



C75 H64 O46; Mol wt: 1701.2850

ACTION – Immunomodulator, a dimeric gallotannin analogue proven to inhibit endotoxin-induced TNF- α production from human peripheral blood mononuclear cells (30% inhibition at 5 μ M). Comparable results were obtained *in vivo*, where a dose of 12.5 mg/kg by infusion decreased TNF- α levels by approximately 50%. Compound lacked IL-1 β -stimulating activity both *in vitro* and *in vivo*. Potentially useful for the treatment of septic shock. Another related compound is:



314332: C82 H62 O46

SOURCE – Pennsylvania State University, Hershey, PA (US).

REFERENCES

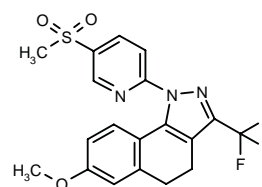
1. Feldman, K.S. (Penn State Research Foundation) *Gallotannins and ellagitannins as regulators of cytokine release*. WO 0136436.
2. Feldman, K.S. et al. *In vitro and in vivo inhibition of LPS-induced tumor necrosis factor- α production by dimeric gallotannin analogues*. Bioorg Med Chem 2002, 10(1): 47.

TREATMENT OF MUSCULOSKELETAL AND CONNECTIVE TISSUE DISEASES

ANTIARTHRITIC DRUGS

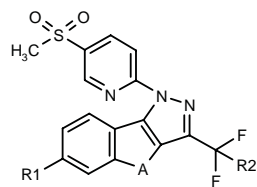
310615

7-Methoxy-1-[5-(methylsulfonyl)pyridin-2-yl]-3-(trifluoromethyl)-4,5-dihydro-1*H*-benzo[*g*]indazole

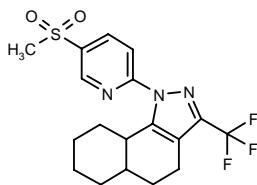


C19 H16 F3 N3 O3 S; Mol wt: 423.4134

ACTION – A selective cyclooxygenase type 2 (COX-2) inhibitor, considered to have potential in a broad range of inflammatory conditions including arthritis, fever, the common cold, dysmenorrhea, inflammatory bowel disease, Crohn's disease, emphysema, acute respiratory distress syndrome, asthma, bronchitis, chronic obstructive pulmonary disease, Alzheimer's disease, transplant rejection, cachexia, allergy, etc. Other specifically claimed pyrazole derivatives are:



Compound	R1	R2	A	Formula
310617	H	F	-(CH2)2-	C ₁₈ H ₁₄ F ₃ N ₃ O ₂ S
310619	OMe	F	-CH2-	C ₁₈ H ₁₄ F ₃ N ₃ O ₃ S
310620	OMe	H	-(CH2)2-	C ₁₉ H ₁₇ F ₂ N ₃ O ₃ S



310621: C18 H20 F3 N3 O2 S

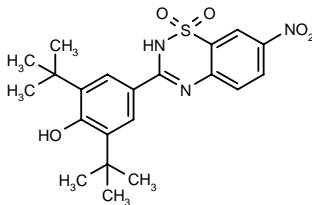
SOURCE – Pfizer.

REFERENCES

1. Sakya, S.M. (Pfizer Products Inc.) *Pyrazole derivs. as anti-inflammatory/analgesic agents*. EP 1142889, JP 2001316387.

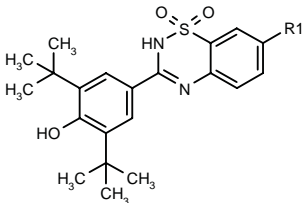
311053

2,6-Di-*tert*-butyl-4-(7-nitro-1,1-dioxo-2*H*-1,2,4-benzothia-diazin-3-yl)phenol



C21 H25 N3 O5 S; Mol wt: 431.5105

ACTION – Antiinflammatory agent, a selective cyclo-oxygenase type 2 (COX-2) inhibitor (46.7% inhibition of 6-keto-PGF_{1α} in endotoxin-activated J774.2 macrophages at 100 μM) proven to inhibit carrageenan-induced rat paw edema by 43.5% at 20 mg/kg p.o., while being devoid of ulcerogenic activity. Other related compounds are:



Compound	R1	Formula
311051	Cl	C ₂₁ H ₂₅ ClN ₂ O ₃ S
311052	Br	C ₂₁ H ₂₅ BrN ₂ O ₃ S

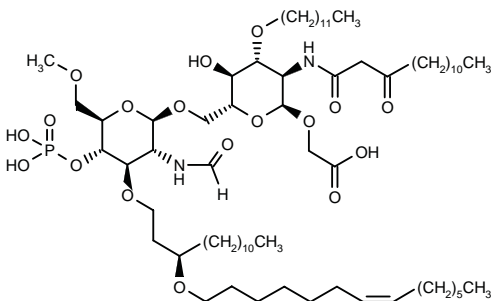
SOURCE – Università degli Studi di Modena, Modena (IT).

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1. Vezzalini, F. et al. *Novel COX-2 inhibitory drugs: Pharmacological and biochemical evaluation*. 30th Congr Naz Soc Ital Farmacol (May 30-June2, Genova) 2001, Abst A14.

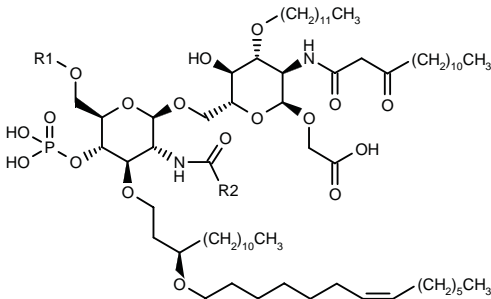
311836

2-[2-Deoxy-6-*O*-[2-deoxy-2-formamido-6-*O*-methyl-4-*O*-phosphono-3-*O*-[3(*R*)-[7(*Z*)-tetradecenyl]oxy]tetradecyl]-β-D-glucopyranosyl]-3-*O*-dodecyl-2-(3-oxotetradecan-amido)-α-D-glucopyranosyloxy]acetic acid



C70 H131 N2 O18 P; Mol wt: 1319.7750

ACTION – Agent with the ability to inhibit macrophage activity, proven to inhibited lipopolysaccharide-induced TNF-α production in TPA-treated human monocytic U-397 cells with an IC₅₀ of 0.005 nM, while showing no toxicity at concentrations up to 5000 nM. Potentially useful as an antiinflammatory, immunosuppressant and antiseptic agent, as well as in the treatment of autoimmune diseases. Other exemplified carboxymethyl-substituted lipid A analogues are:



Compound	R1	R2	Formula
311837	H	H	C ₆₉ H ₁₂₉ N ₂ O ₁₈ P
311839	H	Me	C ₇₀ H ₁₃₁ N ₂ O ₁₈ P
311840	Me	Me	C ₇₁ H ₁₃₃ N ₂ O ₁₈ P

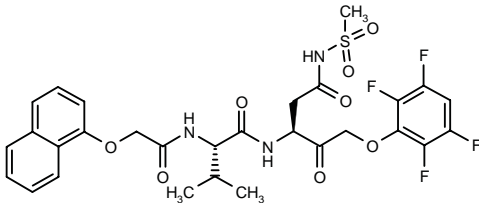
SOURCE – Sankyo.

REFERENCES

1. Watanabe, Y. and Shiozaki, M. (Sankyo Co., Ltd.) *1-Carboxymethyl analogues of lipid A*. JP 2001348396, WO 0177133.

312211

*N*¹-[1(*S*)-[*N*-(Methylsulfonyl)carbamoylmethyl]-2-oxo-3-(2,3,5,6-tetrafluorophenoxy)propyl]-*N*²-[2-(naphthalen-1-yloxy)acetyl]-L-valinamide



C29 H29 F4 N3 O8 S; Mol wt: 655.6191

ACTION – A peptidomimetic compound that acts as an inhibitor of the ICE (IL-1β-converting enzyme)/ced-3 family of cysteine proteases. It inhibited caspases 1, 3, 6 and 8 with *K*_i values of 0.20, 0.08, 0.40 and 0.60 μM, respectively. Potentially useful for the treatment of autoimmune, inflammatory and neurodegenerative diseases, for the prevention of ischemic injury, as well as for preserving organs and cells for use in transplantation.

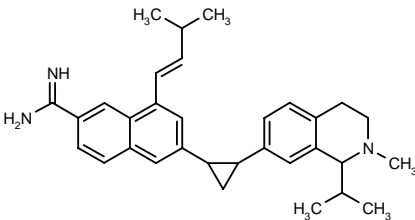
SOURCE – Idun Pharmaceuticals.

REFERENCES

1. Ternansky, R.J. et al. (Idun Pharmaceuticals, Inc.) *Inhibitors of the ICE/ced-3 family of cysteine proteases*. WO 0179162.

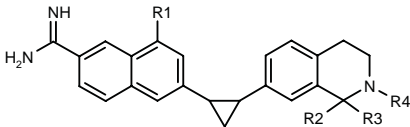
312375

6-[2-(1-Isopropyl-2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)cyclopropyl]-8-[3-methyl-1(*E*)-butenyl]naphthalene-2-carboxamide

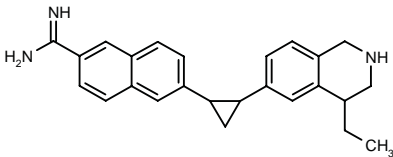


C32 H39 N3; Mol wt: 465.6811

ACTION – Urokinase inhibitor (*K*_i = 0.010 μM) with antiangiogenic activity, potentially useful for the treatment of arthritis, inflammation, angiogenesis-dependent retinopathy, contraception and cancer. Other exemplified naphthamidines include the following:



Compound	R1	R2	R3	R4	Formula
312376	3-furyl	i-Pr	H	Me	C ₃₁ H ₃₃ N ₃ O
312377	(<i>E</i>)-CH=CHCH ₂ OMe	i-Pr	H	Me	C ₃₁ H ₃₇ N ₃ O
312378	(<i>E</i>)-CH=CHCH(Me) ₂	i-Pr	bond		C ₃₁ H ₃₅ N ₃
312379	H	cyclohexyl	H	Me	C ₃₀ H ₃₆ N ₃
312380	vinyl	i-Pr	H	Me	C ₂₉ H ₃₃ N ₃



312381: C25 H27 N3

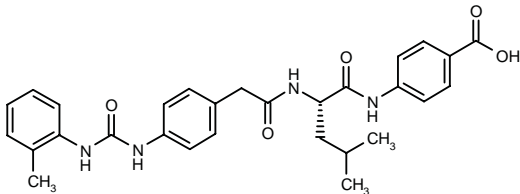
SOURCE – Abbott.

REFERENCES

1. Bruncko, M. et al. (Abbott Laboratories Inc.) *Naphthamide urokinase inhibitors*. WO 0181314.

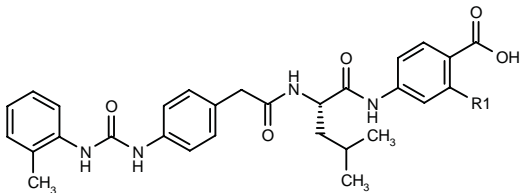
312489

*N*¹-(4-Carboxyphenyl)-*N*²-[2-[4-[3-(2-methylphenyl)-ureido]phenyl]acetyl]-L-leucinamide

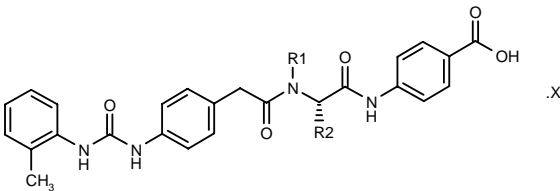


C29 H32 N4 O5; Mol wt: 516.5948

ACTION – Peptidomimetic compound that acts as an α₄β₁, α₄β₇ and/or α₉β₁ integrin antagonist. It inhibited the adhesion of Jurkat cells to VCAM-1-coated plates with an IC₅₀ < 0.5 μM. Potentially useful for the treatment of atherosclerosis, asthma, chronic obstructive pulmonary disease, allergies, diabetes, inflammatory bowel disease, multiple sclerosis, myocardial ischemia, rheumatoid arthritis and transplant rejection, among other inflammatory, immune and autoimmune disorders. Other exemplified compounds are:



Compound	R1	Formula
312490	Cl	C ₂₉ H ₃₁ ClN ₄ O ₅
312491	NHPh	C ₃₅ H ₃₇ N ₅ O ₅
312492	OPh	C ₃₅ H ₃₆ N ₄ O ₆



Compound	R1	R2	X	Formula
312493	H	(CH ₂) ₄ NH ₂	CF ₃ CO ₂ H	C ₂₉ H ₃₃ N ₅ O ₅ ·C ₂ HF ₃ O ₂
312495	(CH ₂) ₃ OMe	H		C ₂₉ H ₃₂ N ₄ O ₆

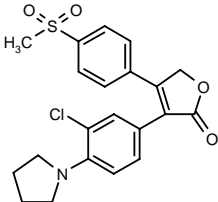
SOURCE – Bayer.

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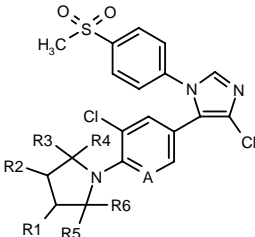
312616

3-[3-Chloro-4-(1-pyrrolidinyl)phenyl]-4-[4-(methylsulfonyl)-phenyl]furan-2(5*H*)-one

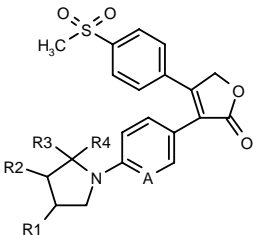


C21 H20 Cl N O4 S; Mol wt: 417.9110

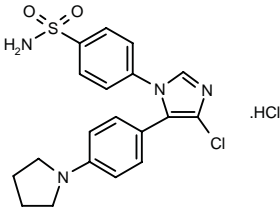
ACTION – Antiinflammatory agent that acts as a selective cyclooxygenase type 2 (COX-2) inhibitor. The compound inhibited COX-2 by 93% at 0.1 μM, while no effect was observed against COX-1 at the same concentration. Other exemplified heterocyclic compounds are:



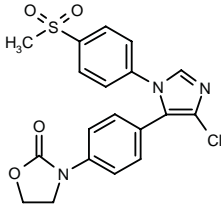
Compound	R1	R2	R3	R4	R5	R6	A	Formula
312617	H	H	H	H	H	H	CH	C ₂₀ H ₂₀ ClN ₃ O ₂ S
312618	OH	H	H	H	H	H	CH	C ₂₀ H ₂₀ ClN ₃ O ₃ S
312621	H	H	H	H	H	Me	CH	C ₂₁ H ₂₂ ClN ₃ O ₂ S
312625	H	H	H	H	H	H	CH	C ₂₀ H ₁₉ Cl ₂ N ₃ O ₂ S
312626	H	H	-O-		-O-		CH	C ₂₀ H ₁₆ ClN ₃ O ₄ S
312629	bond		-O-		H	H	CH	C ₂₀ H ₁₆ ClN ₃ O ₃ S
312631	H	H	H	H	-O-		CH	C ₂₀ H ₁₈ ClN ₃ O ₃ S
312632	H	H	H	H	H	H	N	C ₁₉ H ₁₉ ClN ₄ O ₂ S



Compound	R1	R2	R3	R4	A	Formula
312633	bond		-O-		CH	C ₂₁ H ₁₇ NO ₅ S
312634	H	H	H	H	CH	C ₂₁ H ₂₁ NO ₄ S
312635	H	H	H	H	N	C ₂₀ H ₂₀ N ₂ O ₄ S



312623: C19 H19 Cl N4 O2 S . HCl



312630: C19 H16 Cl N3 O4 S

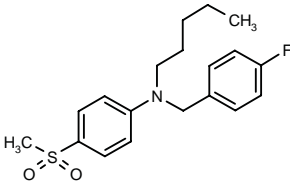
SOURCE – Uriach.

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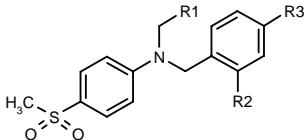
312723

N-(4-Fluorobenzyl)-*N*-[4-(methylsulfonyl)phenyl]-*N*-pentylamine



C19 H24 F N O2 S; Mol wt: 349.4676

ACTION – Antiinflammatory and analgesic agent, a cyclooxygenase type 2 (COX-2) inhibitor with IC₅₀ values of < 0.20 and > 40 μM for COX-2 and COX-1, respectively. Other exemplified *p*-sulfonyl-aryl and -heteroaryl-amines include the following:



Compound	R1	R2	R3	Formula
312724	Et	H	F	C ₁₇ H ₂₀ FNO ₂ S
312725	cyclopropyl	H	F	C ₁₈ H ₂₀ FNO ₂ S
312726	Pr	OMe	H	C ₁₉ H ₂₅ NO ₃ S
312727	Pr	H	Cl	C ₁₈ H ₂₂ ClNO ₂ S
312728	Pr	H	OMe	C ₁₉ H ₂₅ NO ₃ S
312729	Pr	F	F	C ₁₈ H ₂₁ F ₂ NO ₂ S

SOURCE – Roche.

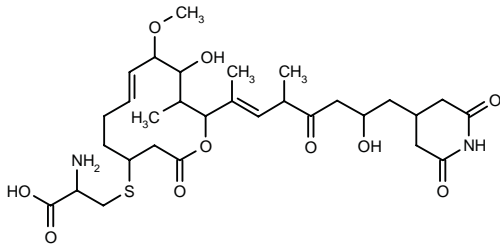
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NK-30424B

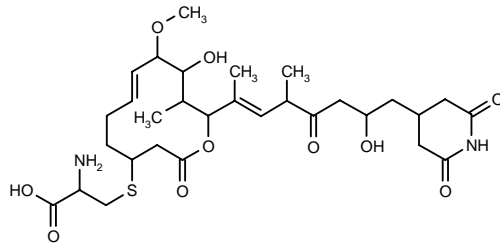
313850

(+)-2-Amino-3-[12-[7-(2,6-dioxopiperidin-4-yl)-6-hydroxy-1,3-dimethyl-4-oxo-1-heptenyl]-10-hydroxy-9-methoxy-11-methyl-2-oxooxacyclododec-7-en-4-ylsulfanyl]propionic acid isomer B



C30 H46 N2 O10 S; Mol wt: 626.7634

ACTION – Inhibitor of lipopolysaccharide (LPS)-induced TNF- α production (IC_{50} = 0.9 μ M in murine L929 cells) isolated from the fermentation broth of *Streptomyces* sp. NA30424. Compound also inhibited the LPS-induced TNF- α promoter activities in Jurkat J774.1 cells (IC_{50} = 0.44 μ M). Potentially useful for the treatment of rheumatoid arthritis, multiple sclerosis and cancer. Another related compound is:



NK-30424A [313847]: C30 H46 N2 O10 S: Isomer A

SOURCE – Nippon Kayaku.

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3. Takayasu, Y. et al. *NK30424A and B, novel inhibitors of lipopolysaccharide-induced tumour necrosis factor alpha production, produced by Streptomyces sp. NA30424.* J Antibiot 2001, 54(12): 1111.

TREATMENT OF OTHER
AUTOIMMUNE DISORDERS

ABETIMUS SODIUM

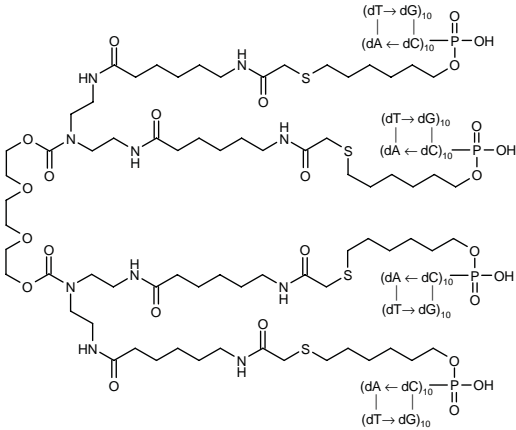
Prop INN; USAN

217652

Deoxyribonucleic acid d(C-A-C-A-C-A-C-A-C-A-C-A-C-A-C-A-C-A-C-A-C-A), 5'-ester with 1,2-ethanediylbis(oxy-2,1-ethanediyl)bis[2-(21,21-dihydroxy-4,11-dioxo-20-oxa-13-thia-3,10-diaza-21-phosphaeneicos-1-yl)-23,23-dihydroxy-6,13-dioxo-22-oxa-15-thia-2,5,12-triaza-23-phosphatricosanoate] (4:1), P,P',23,23'-tetraoxide, complex with deoxyribonucleic acid d(T-G-T-G-T-G-T-G-T-G-T-G-T-G-T-G-T-G-T-G-T-G) (1:1), hexapentacontahectasodium salt

DNA d(C-A-C-A-C-A-C-A-C-A-C-A-C-A-C-A-C-A-C-A-C-A), 5'-ester with 1,2-ethanediylbis(oxy-2,1-ethanediyl)bis[2-(21,21-dihydroxy-21-oxido-4,11-dioxo-20-oxa-13-thia-3,10-diaza-21-phosphaheneicos-1-yl)-23,23-dihydroxy-23-oxido-6,13-dioxo-22-oxa-15-thia-2,5,12-triaza-23-phosphatricosanoate] (4:1), complex with DNA d(T-G-T-G-T-G-T-G-T-G-T-G-T-G-T-G-T-G-T-G-T-G) (1:1), hexapentacontahectasodium salt

LJP-394
Rentol



C1632 H1944 N610 Na156 O970 P156 S4

ACTION – Immunosuppressant, a tetrakis-oligonucleotide conjugate proven active in a murine model of systemic lupus erythematosus (SLE). In a phase II trial in patients with inactive or mild SLE, compound (1, 10 and 50 mg i.v. once or twice weekly or once monthly) was well tolerated and the greatest reduction in anti-dsDNA antibody titers was found in patients receiving a dose of 50 mg/week. Data from an earlier phase II/III clinical trial indicate that treatment with LJP-394 appeared to be as effective as current immunosuppressive therapy in reducing antibodies to double-stranded DNA, which are believed to be responsible for lupus renal disease.

SOURCE – La Jolla Pharmaceutical.

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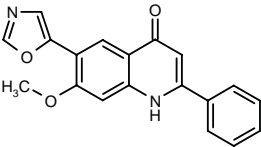
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MONOGRAPH – Sorbera, L.A. et al. *Abetimus Sodium*. *Drugs Fut* 2001, 26(7): 0633.

IMMUNOMODULATING AGENTS

312442

7-Methoxy-6-(5-oxazolyl)-2-phenylquinolin-4(1H)-one



C19 H14 N2 O3; Mol wt: 318.3306

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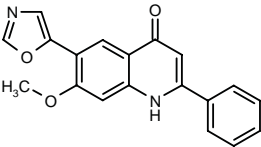
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MONOGRAPH – Sorbera, L.A. et al. *Abetimus Sodium*. *Drugs Fut* 2001, 26(7): 0633.

IMMUNOMODULATING AGENTS

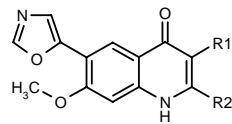
312442

7-Methoxy-6-(5-oxazolyl)-2-phenylquinolin-4(1H)-one



C19 H14 N2 O3; Mol wt: 318.3306

ACTION – An inhibitor of IMP dehydrogenase (IMPDH), particularly useful for the treatment of transplant rejection and autoimmune diseases. Other specifically claimed heterocyclic compounds include the following:



Compound	R1	R2	Formula
312443	H	3-Br-Ph	C ₁₉ H ₁₃ BrN ₂ O ₃
312444	H	3-[PhCH ₂ OC(=O)N(Me)]-5-indanyl	C ₃₁ H ₂₇ N ₃ O ₅
312445	H	3-[N(Me)CH ₂ CH ₂ O]-Ph	C ₂₃ H ₂₃ N ₃ O ₄
312446	OH	4-Cl-3-Me-Ph	C ₂₀ H ₁₅ ClN ₂ O ₄
312447	H	2(R)-(i-PrNHCOO)-3(R)-N(Me)2-5-indanyl	C ₂₈ H ₃₀ N ₄ O ₅
312448	H	3-(4-morpholinyl-CH ₂ CH ₂ O)-4-Me-Ph	C ₂₆ H ₂₇ N ₃ O ₅
312449	OH	3-N(Me)2-5-indanyl	C ₂₄ H ₂₃ N ₃ O ₄
312450	H	N(Me)2	C ₁₅ H ₁₅ N ₃ O ₃
312451	H	1-(1-pyrrolidinyl)-5-indanyl	C ₂₆ H ₂₅ N ₃ O ₃

SOURCE – Bristol-Myers Squibb.

REFERENCES

1. Iwanowicz, E.J. et al. (Bristol-Myers Squibb Co.) *Heterocycles that are inhibitors of IMPDH enzyme*. WO 0181340.

V12.PF3.1

313771

Preerythrocytic recombinant malaria vaccine containing circumsporozoite protein (CSP)-specific neutralizing B-cell epitopes and a universal T-cell epitope, combined with the highly immunogenic hepatitis B core antigen (HBcAg) as the carrier platform

ACTION – Preerythrocytic malaria vaccine consisting of *Plasmodium falciparum* circumsporozoite protein (CSP)-specific neutralizing B- and T-cell epitopes combined with the hepatitis B core antigen (HBcAg) as the carrier platform. In mice, the vaccine given i.p. produced very high levels of sporozoite-binding antibodies (ELISA titer > 10⁶) following a primary dose of 20 µg in complete Freund's adjuvant and a booster dose of 10 µg in incomplete Freund's adjuvant. The antibodies persisted at high levels for over 10 months after the first immunization and represented all IgG isotypes. No genetic non-responders or low responders were identified and the vaccine induced a broad range of T-cell specificities, including malaria-specific T-cells.

SOURCES – Karolinska Institute, Stockholm (SE); Vaccine Research Institute of San Diego, San Diego, CA (US).

REFERENCES

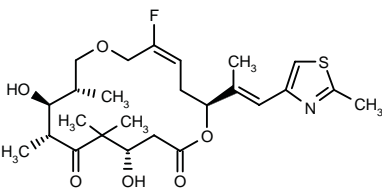
1. Milich, D.R. et al. *Conversion of poorly immunogenic malaria repeat sequences into highly immunogenic vaccine candidate*. Vaccine 2001, 20(5-6): 771.

ONCOLYTIC DRUGS

ANTIMITOTIC DRUGS

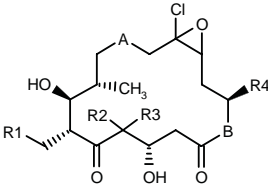
312541

(4*S*,7*R*,8*S*,9*S*,13*Z*,16*S*)-4,8-Dihydroxy-13-fluoro-16-[(*E*)-1-methyl-2-(2-methylthiazol-4-yl)vinyl]-5,5,7,9-tetra-methyl-1,11-dioxacyclohexadec-13-ene-2,6-dione

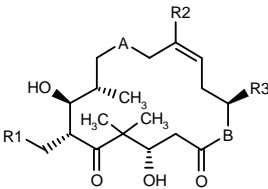


C25 H36 F N O6 S; Mol wt: 497.6244

ACTION – Epothilone derivative that interacts with tubulin and stabilizes formed microtubules. Potentially useful for the treatment of tumors, as well as for antiangiogenic therapy and for the treatment of chronic inflammatory disorders. Other specifically claimed compounds are:



Compound	R1	R2	R3	R4	A	B	Formula
312542	H	-(CH ₂) ₃ -		(Z)-2-Me-4-thiazolyl-CH=C(F)	O	O	C ₂₅ H ₃₃ ClFNO ₇ S
312546	H	Me	Me	2-Me-5-benzothiazolyl	O	NH	C ₂₆ H ₃₅ ClN ₂ O ₆ S
312548	H	Me	Me	2-Me-5-benzothiazolyl	CH ₂	NH	C ₂₇ H ₃₇ ClN ₂ O ₅ S
312549	vinyl	Me	Me	2-Me-5-benzothiazolyl	CH ₂	NH	C ₂₉ H ₃₉ ClN ₂ O ₅ S



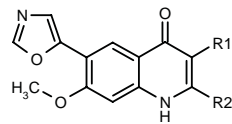
Compound	R1	R2	R3	A	B	Formula
312543	H	Cl	2-Me-5-benzoxazolyl	O	O	C ₂₆ H ₃₄ ClNO ₇
312544	H	F	2-Me-5-benzothiazolyl	CH2	O	C ₂₇ H ₃₆ FNO ₅ S
312545	H	Cl	(E)-2-Pyr-CH=C(Me)	O	NH	C ₂₆ H ₃₇ ClN ₂ O ₅
312547	Me	Cl	(Z)-2-Pyr-CH=C(Cl)	CH2	NH	C ₂₇ H ₃₈ Cl ₂ N ₂ O ₄

SOURCE – Schering AG.

REFERENCES

1. Buchmann, B. et al. (Schering AG) *Novel epothilone derivs., method for the preparation thereof and their pharmaceutical use*. DE 10020517, WO 0181342.

ACTION – An inhibitor of IMP dehydrogenase (IMPDH), particularly useful for the treatment of transplant rejection and autoimmune diseases. Other specifically claimed heterocyclic compounds include the following:



Compound	R1	R2	Formula
312443	H	3-Br-Ph	C ₁₉ H ₁₃ BrN ₂ O ₃
312444	H	3-[PhCH ₂ OC(=O)N(Me)]-5-indanyl	C ₃₁ H ₂₇ N ₃ O ₅
312445	H	3-[N(Me)2CH ₂ CH ₂ O]-Ph	C ₂₃ H ₂₃ N ₃ O ₄
312446	OH	4-Cl-3-Me-Ph	C ₂₀ H ₁₅ ClN ₂ O ₄
312447	H	2(R)-(i-PrNHCOO)-3(R)-N(Me)2-5-indanyl	C ₂₈ H ₃₀ N ₄ O ₅
312448	H	3-(4-morpholinyl-CH ₂ CH ₂ O)-4-Me-Ph	C ₂₆ H ₂₇ N ₃ O ₅
312449	OH	3-N(Me)2-5-indanyl	C ₂₄ H ₂₃ N ₃ O ₄
312450	H	N(Me)2	C ₁₅ H ₁₅ N ₃ O ₃
312451	H	1-(1-pyrrolidinyl)-5-indanyl	C ₂₆ H ₂₅ N ₃ O ₃

SOURCE – Bristol-Myers Squibb.

REFERENCES

1. Iwanowicz, E.J. et al. (Bristol-Myers Squibb Co.) *Heterocycles that are inhibitors of IMPDH enzyme*. WO 0181340.

V12.PF3.1

313771

Preerythrocytic recombinant malaria vaccine containing circumsporozoite protein (CSP)-specific neutralizing B-cell epitopes and a universal T-cell epitope, combined with the highly immunogenic hepatitis B core antigen (HBcAg) as the carrier platform

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SOURCES – Karolinska Institute, Stockholm (SE); Vaccine Research Institute of San Diego, San Diego, CA (US).

REFERENCES

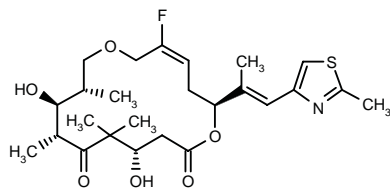
1. Milich, D.R. et al. *Conversion of poorly immunogenic malaria repeat sequences into highly immunogenic vaccine candidate*. Vaccine 2001, 20(5-6): 771.

ONCOLYTIC DRUGS

ANTIMITOTIC DRUGS

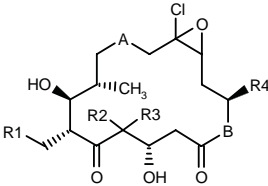
312541

(4*S*,7*R*,8*S*,9*S*,13*Z*,16*S*)-4,8-Dihydroxy-13-fluoro-16-[(*E*)-1-methyl-2-(2-methylthiazol-4-yl)vinyl]-5,5,7,9-tetra-methyl-1,11-dioxacyclohexadec-13-ene-2,6-dione

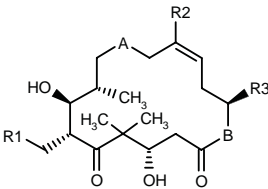


C25 H36 F N O6 S; Mol wt: 497.6244

ACTION – Epothilone derivative that interacts with tubulin and stabilizes formed microtubules. Potentially useful for the treatment of tumors, as well as for antiangiogenic therapy and for the treatment of chronic inflammatory disorders. Other specifically claimed compounds are:



Compound	R1	R2	R3	R4	A	B	Formula
312542	H	-(CH ₂) ₃ -		(Z)-2-Me-4-thiazolyl-CH=C(F)	O	O	C ₂₅ H ₃₃ ClFNO ₇ S
312546	H	Me	Me	2-Me-5-benzothiazolyl	O	NH	C ₂₆ H ₃₅ ClN ₂ O ₆ S
312548	H	Me	Me	2-Me-5-benzothiazolyl	CH ₂	NH	C ₂₇ H ₃₇ ClN ₂ O ₅ S
312549	vinyl	Me	Me	2-Me-5-benzothiazolyl	CH ₂	NH	C ₂₉ H ₃₉ ClN ₂ O ₅ S



Compound	R1	R2	R3	A	B	Formula
312543	H	Cl	2-Me-5-benzoxazolyl	O	O	C ₂₆ H ₃₄ ClNO ₇
312544	H	F	2-Me-5-benzothiazolyl	CH2	O	C ₂₇ H ₃₆ FNO ₅ S
312545	H	Cl	(E)-2-Pyr-CH=C(Me)	O	NH	C ₂₆ H ₃₇ ClN ₂ O ₅
312547	Me	Cl	(Z)-2-Pyr-CH=C(Cl)	CH2	NH	C ₂₇ H ₃₈ Cl ₂ N ₂ O ₄

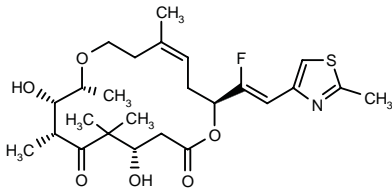
SOURCE – Schering AG.

REFERENCES

1. Buchmann, B. et al. (Schering AG) *Novel epothilone derivs., method for the preparation thereof and their pharmaceutical use*. DE 10020517, WO 0181342.

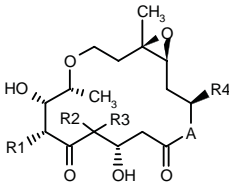
312550

(4*S*,7*R*,8*S*,9*R*,16*S*)-16-[(*Z*)-1-Fluoro-2-(2-methylthiazol-4-yl)vinyl]-4,8-dihydroxy-5,5,7,9,13-pentamethyl-1,10-dioxacyclohexadec-13(*Z*)-ene-2,6-dione

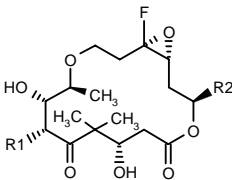


C25 H36 F N O6 S; Mol wt: 497.6244

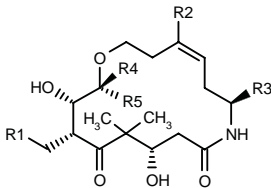
ACTION – Epothilone derivative that interacts with tubulin and stabilizes formed microtubules. Potentially useful for the treatment of tumors, as well as for antiangiogenic therapy and for the treatment of chronic inflammatory disorders. Other specifically claimed compounds are:



Compound	R1	R2	R3	R4	A	Formula
312551	allyl	Me	Me	(<i>Z</i>)-2-Me-4-thiazolyl-CH=C(F)	NH	C ₂₇ H ₃₉ FN ₂ O ₆ S
312553	allyl	-(CH2)3-		(<i>Z</i>)-2-Me-4-thiazolyl-CH=C(Me)	O	C ₂₉ H ₄₁ NO ₇ S
312554	2-butyryl	Me	Me	(<i>Z</i>)-2-Pyr-CH=C(Me)	O	C ₃₀ H ₄₁ NO ₇
312555	2-butyryl	-(CH2)3-		2-Me-5-benzoxazolyl	NH	C ₃₁ H ₄₀ N ₂ O ₇



Compound	R1	R2	Formula
312556	Et	(<i>E</i>)-2-Me-4-thiazolyl-CH=C(Me)	C ₂₆ H ₃₈ FNO ₇ S
312557	Me	2-Me-5-benzoxazolyl	C ₂₆ H ₃₄ FNO ₈



Compound	R1	R2	R3	R4	R5	Formula
312552	Me	Me	(<i>Z</i>)-2-Pyr-CH=C(Cl)	H	Me	C ₂₇ H ₃₉ ClN ₂ O ₅
312558	H	F	2-Me-5-benzothiazolyl	Me	H	C ₂₆ H ₃₅ FN ₂ O ₅ S

SOURCE – Schering AG.

REFERENCES

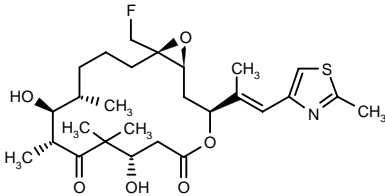
1. Schwede, W. et al. (Schering AG) 9-Oxa-epothilon derivs., method for the production and use thereof in pharmaceutical preparations. DE 10020899, WO 0181341.

26-FLUOROEPOTHILONE B

301741

(1*S*,3*S*,7*S*,10*R*,11*S*,12*S*,16*R*)-16-(Fluoromethyl)-7,11-dihydroxy-8,8,10,12-tetramethyl-3-[1(*E*)-methyl-2-(2-methylthiazol-4-yl)vinyl]-4,17-dioxabicyclo[14.1.0]-heptadecane-5,9-dione

CGP-85715



C27 H40 F N O6 S; Mol wt: 525.6780

ACTION – Antineoplastic agent, a C26-fluoro derivative of epothilone B with cytotoxic activity against human prostate cancer cell lines PC-3, LNCaP, MDA PCA 2a and MDA PCA 2b (IC₅₀ = 0.6, 1.2, 2.8 and 2.7 nM, respectively). *In vivo* in mice bearing prostate cancer MDA PCA 2b and PC-3, compound (2-10 mg/kg i.v.) produced a sustained and dose-dependent decrease in tumor growth (53-80% after 30 days of treatment); for comparison, paclitaxel at the maximally tolerated dose of 40 mg/kg produced only minimal inhibition of tumor growth.

SOURCES – Novartis; Scripps Research Institute, La Jolla, CA (US).

REFERENCES

1. Nicolaou, C.K. et al. (Novartis AG;Scripps Research Institute) *Epothilone analogs*. JP 2001504856, WO 9825929.

2. Altmann, K.-H. et al. *Antitumor activity profile of the epothilone B-derivative CGP 85715*. Proc Amer Assoc Cancer Res 2001, 42: Abst 1979.

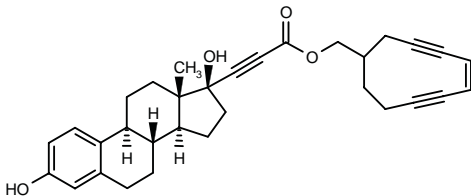
3. Briggs, J.M. and Lee, K.W. *Comparative molecular field analysis (coMFA) study of epothilones-tubulin depolymerization inhibitors: Pharmacophore development using 3D QSAR methods*. J Comput-Aided Mol Des 2001, 15(1): 41.

4. Newman, R.A. et al. *Antitumor efficacy of 26-fluoroepothilone B against human prostate cancer xenografts*. Cancer Chemother Pharmacol 2001, 48(4): 319.

HORMONAL AGENTS

311201

3-[3,17β-Dihydroxyestra-1(10),2,4-trien-17-yl]-2-propynoic acid cyclodec-5-en-3,7-diyn-1-ylmethyl ester



C32 H34 O4; Mol wt: 482.6166

ACTION – Cytotoxic antiestrogen, an estrogen-enediynes conjugate proven to bind to and induce proteolysis of the human estrogen receptor ER α , and consequently to reduce the transcriptional activity of estradiol in breast cancer T-47D cells. Compound exhibited strong cytotoxic activity in hER α -rich breast cancer MCF-7 cells (IC₅₀ = 31 μ M), but was also active in hER α -deficient MDA-MB-231 cells (IC₅₀ = 48 μ M) or androgen receptor-negative HEK 293 cells (IC₅₀ = 10 μ M), indicating an independent cytotoxic mechanism. Potentially useful for the treatment of breast cancer.

SOURCES – Beth Israel Deaconess Medical Center, Boston, MA (US); Clemson University, Clemson, SC (US); Dana-Farber Cancer Institute, Boston, MA (US); Harvard Medical School, Boston, MA (US); Northwestern University, Evanston, IL (US).

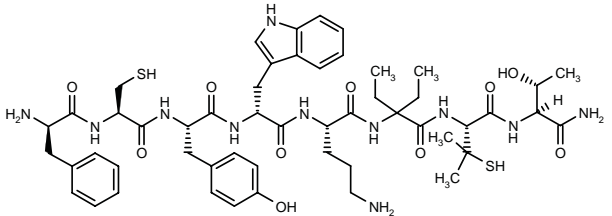
REFERENCES

1. Jones, G.B. et al. *Protein-degrading enediynes: Library screening of Bergman cycloaromatization products*. Org Lett 2000, 2(13): 1863.

2. Jones, G.B. et al. *Target-directed enediynes: Design estramycins*. J Org Chem 2001, 66(1): 3688.

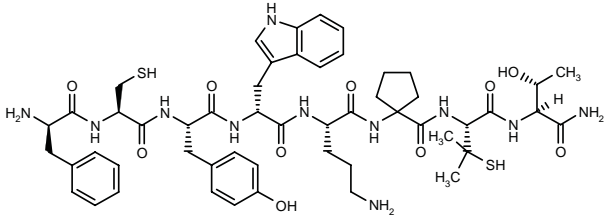
312415

D-Phenylalanyl-L-cysteinyl-L-tyrosyl-D-tryptophyl-L-ornithyl-2,2-diethylglycyl-L-penicillaminyl-L-threoninamide



C52 H73 N11 O10 S2; Mol wt: 1076.3480

ACTION – Somatostatin analogue, potentially useful for the treatment of cancer. It demonstrated activity against human colon adenocarcinoma xenografts in nude mice, with 57.1% inhibition of tumor growth on day 21 after a 10-day treatment with 85 μ g/ml i.v. Another exemplified somatostatin analogue is:



312416: C52 H71 N11 O10 S2

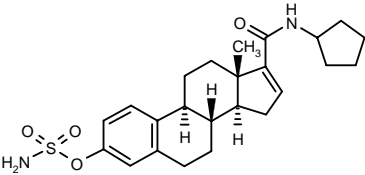
SOURCE – Dabur Research Foundation.

REFERENCES

1. Burman, A.C. et al. (Dabur Research Foundation) *Somatostatin analogs for the treatment of cancer*. US 6316414.

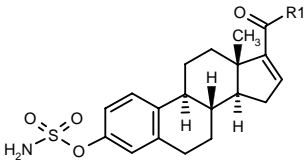
312931

Sulfamic acid 17-(N-cyclopentylcarbamoyl)estra-1,3,5(10),16-tetraen-3-yl ester



C24 H32 N2 O4 S; Mol wt: 444.5928

ACTION – Steroid sulfatase inhibitor (IC₅₀ = 1.0 nM), potentially useful for the treatment of estrogen-dependent tumors including breast, uterine, ovarian and prostate cancer. Other exemplified estra-1,3,5(10)-triene derivatives are:



Compound	R1	Formula
312932	1-pyrrolidinyl	C ₂₃ H ₃₀ N ₂ O ₄ S
312933	4-(2-Pyr)-1-Piz	C ₂₈ H ₃₄ N ₄ O ₄ S
312934	cyclopropyl-CH2NH	C ₂₃ H ₃₀ N ₂ O ₄ S
312935	NHCH2CH2OMe	C ₂₂ H ₃₀ N ₂ O ₅ S
312936	6-MeO-3-Pyr-NH	C ₂₅ H ₂₉ N ₃ O ₅ S

SOURCE – Kyowa Hakko.

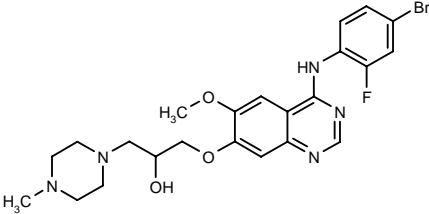
REFERENCES

1. Ino, Y. et al. (Kyowa Hakko Kogyo Co., Ltd.) *Estra-1,3,5(10)-triene derivs*. WO 0181364.

INHIBITORS OF SIGNAL TRANSDUCTION PATHWAYS

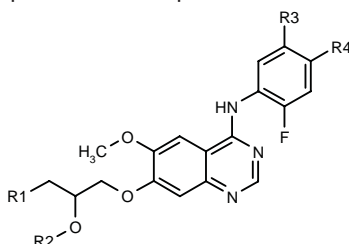
312019

1-[4-(4-Bromo-2-fluorophenylamino)-6-methoxyquinazolin-7-yloxy]-3-(4-methylpiperazin-1-yl)propan-2-ol



C23 H27 Br F N5 O3; Mol wt: 520.4003

ACTION – Receptor tyrosine kinase, particularly vascular endothelial growth factor (VEGF) receptor tyrosine kinase, inhibitor, potentially useful for the treatment of angiogenesis- and/or increased vascular permeability-associated conditions such as cancer, diabetes, psoriasis, rheumatoid arthritis, Kaposi's sarcoma, hemangioma, acute and chronic nephropathies, atherosclerosis, arterial restenosis, autoimmune diseases, acute inflammation, endometriosis, dysfunctional uterine bleeding and ocular diseases with retinal vessel proliferation. Other exemplified quinazoline compounds include the following:



Compound	R1	R2	R3	R4	Formula
312020	1-pyrrolidinyl	H	H	Cl	C ₂₂ H ₂₄ ClFN ₄ O ₃
312021	4-morpholinyl	H	H	Cl	C ₂₂ H ₂₄ ClFN ₄ O ₄
312022	3-thiazolidinyl	H	H	Br	C ₂₁ H ₂₂ BrFN ₄ O ₃ S
312023	4-Pyr-S	H	H	Br	C ₂₃ H ₂₀ BrFN ₄ O ₃ S
312024	1-pyrrolidinyl	H	OH	Cl	C ₂₂ H ₂₄ ClFN ₄ O ₄
312025	1-pyrrolidinyl	Ac	OH	Br	C ₂₄ H ₂₆ BrFN ₄ O ₅
312026	1-pyrrolidinyl	H	OH	Br	C ₂₂ H ₂₄ BrFN ₄ O ₄

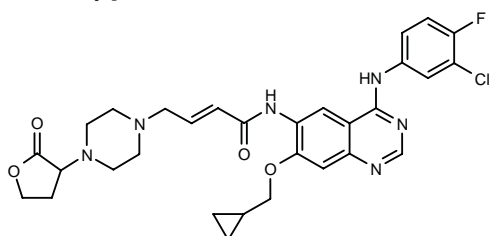
SOURCE – AstraZeneca.

REFERENCES

1. Hennequin, L.F.A. and Stokes, E.S.E. (AstraZeneca AB;AstraZeneca plc) *Quinazoline cpds.* WO 0177085.

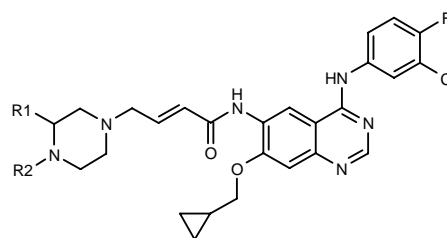
312086

N-[4-(3-Chloro-4-fluorophenylamino)-7-(cyclopropylmethoxy)quinazolin-6-yl]-4-[4-(2-oxotetrahydrofuran-3-yl)piperazin-1-yl]-2-butenamide

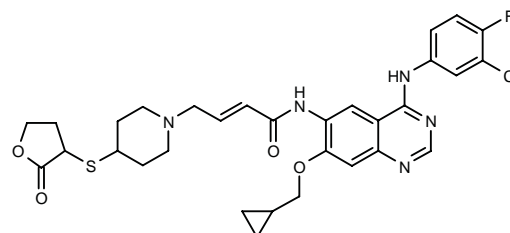


C₃₀H₃₂ClF N₆O₄; Mol wt: 595.0718

ACTION – Tyrosine kinase-mediated signal transduction inhibitor, potentially useful for the treatment of cancer, as well as lung and respiratory tract diseases. This compound inhibited epidermal growth factor (EGF)-dependent proliferation of cells expressing the human EGF receptor with an IC₅₀ of 0.05 nM. Other exemplified bicyclic compounds are:



Compound	R1	R2	Formula
312088	H	5-oxo-2(S)-THF	C ₃₁ H ₃₂ ClFN ₆ O ₅
312089	H	2-oxo-4-THF	C ₃₀ H ₃₂ ClFN ₆ O ₄
312090	H	2-oxo-3-THF-SCH ₂ CH ₂	C ₃₂ H ₃₆ ClFN ₆ O ₄ S
312091		-CH ₂ OCOCH ₂ -	C ₂₉ H ₃₀ ClFN ₆ O ₄
312092		-COOCH ₂ CH ₂ -	C ₂₉ H ₃₀ ClFN ₆ O ₄



312093: C₃₁ H₃₃ Cl F N₅ O₄ S

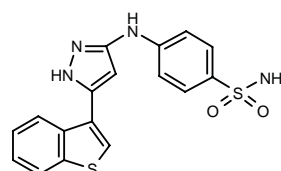
SOURCE – Boehringer Ingelheim.

REFERENCES

1. Himmelsbach, F. et al. (Boehringer Ingelheim Pharma KG) *Bicyclic heterocycles, medicaments containing said cpds., the use thereof and method for producing them.* DE 10017539, WO 0177104.

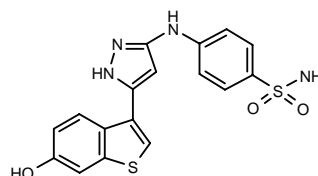
312249

4-[5-(1-Benzothien-3-yl)-1*H*-pyrazol-3-ylamino]benzene-sulfonamide



C₁₇H₁₄N₄O₂S₂; Mol wt: 370.4556

ACTION – Inhibitor of protein kinases, particularly VEGF (vascular endothelial growth factor), CHK1 and the cyclin-dependent kinases CDK2, CDK4 and/or CDK6, potentially useful for the treatment of cancer. Compound gave K_i values of 1.6 and 0.062 μM, respectively, against CDK4/D and CDK2/A kinases. In addition, it inhibited the proliferation of human colon cancer HCT 116 cells with IC₅₀ and IC₉₀ values of 9.5 and 24 μM, respectively. Another exemplified 1*H*-pyrazol-3-amine derivative is:



312252: C₁₇ H₁₄ N₄ O₃ S₂

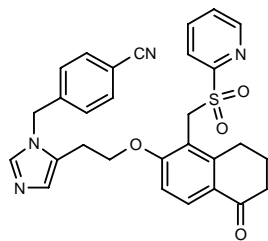
SOURCE – Agouron (Pfizer).

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1. Reich, S.H. and Wallace, M.B. (Agouron Pharmaceuticals, Inc.) *Pyrazoles for inhibiting protein kinase*. WO 0179198.

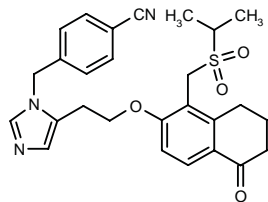
312288

4-[5-[2-[5-Oxo-1-(pyridin-2-ylsulfonylmethyl)-5,6,7,8-tetrahydronaphthalen-2-yloxy]ethyl]-1*H*-imidazol-1-ylmethyl]benzonitrile



C29 H26 N4 O4 S; Mol wt: 526.6144

ACTION – Protein farnesyltransferase inhibitor (IC₅₀ = 0.3 nM), potentially useful for the treatment of proliferative disorders, especially cancer, restenosis and atherosclerosis. Another compound from this series of 1,2,3,4-tetrahydronaphthalen-1-one derivatives is:



312289: C27 H29 N3 O4 S

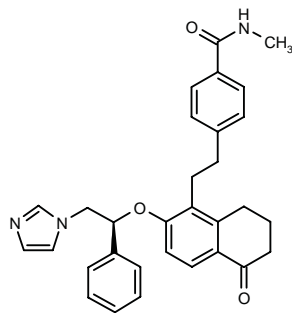
SOURCE – Pfizer.

REFERENCES

1. Leonard, D.M. et al. (Pfizer Inc.) *Dihydro-2H-naphthalene-1-one inhibitors of ras farnesyl transferase*. WO 0179179.

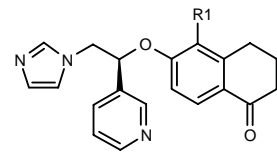
312290

4-[2-[2-[2-(1*H*-Imidazol-1-yl)-1(*S*)-phenylethoxy]-5-oxo-5,6,7,8-tetrahydronaphthalen-1-yl]ethyl]-*N*-methylbenzamide



C31 H31 N3 O3; Mol wt: 493.6039

ACTION – Protein farnesyltransferase inhibitor (IC₅₀ = 0.1 nM), potentially useful for the treatment of proliferative disorders, especially cancer, restenosis and atherosclerosis. Other exemplified 1,2,3,4-tetrahydronaphthalen-1-one derivatives are:



Compound	R1	Formula
312291	2-Pyr-SO2CH2	C ₂₆ H ₂₄ N ₄ O ₄ S
312292	1-isoquinolinyl-CONH	C ₃₀ H ₂₅ N ₅ O ₃

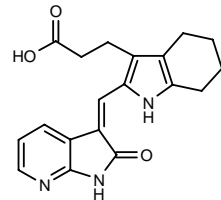
SOURCE – Pfizer.

REFERENCES

1. Denny, W.A. et al. (Pfizer Inc.) *5-Substd. tetralones as inhibitors of ras farnesyl transferase*. WO 0179180.

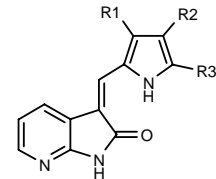
312417

3-[2-(2-Oxo-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-3-ylidenemethyl)-4,5,6,7-tetrahydro-1*H*-indol-3-yl]propionic acid



C19 H19 N3 O3; Mol wt: 337.3771

ACTION – Protein kinase modulator, expected to be useful for the treatment of cancer. The compound inhibited FLK-1, EGF (epidermal growth factor), FGF (fibroblast growth factor) and PDGF (platelet-derived growth factor) receptor kinases with respective IC₅₀ values of 0.14, 12.50, 2.27 and 0.15 μM. Other exemplified bicyclic compounds are:



Compound	R1	R2	R3	Formula
312418	Me	H	Me	C ₁₄ H ₁₃ N ₃ O
312419	H	-(CH2)4-		C ₁₆ H ₁₅ N ₃ O
312420	Me	-(CH2)4-		C ₁₇ H ₁₇ N ₃ O
312421	Me	CH2CH2CO2H	H	C ₁₆ H ₁₅ N ₃ O ₃
312422	Me	CH2CH2CO2H	Me	C ₁₇ H ₁₇ N ₃ O ₃

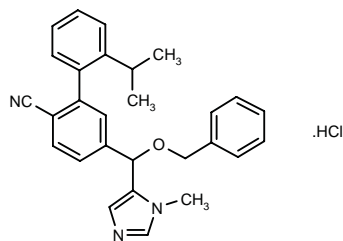
SOURCE – Sugen (Pharmacia).

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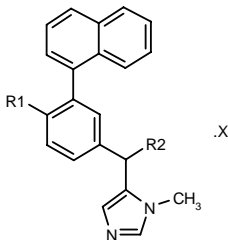
312429

5-[1-(Benzyloxy)-1-(1-methyl-1*H*-imidazol-5-yl)methyl]-2'-isopropylbiphenyl-2-carbonitrile hydrochloride

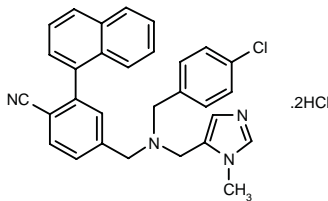


C28 H27 N3 O . HCl; Mol wt: 458.0022

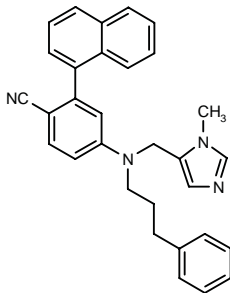
ACTION – Protein farnesyltransferase inhibitor, as demonstrated *in vitro*, with complete inhibition at 1 μM. Potentially useful as an anticancer agent. Other exemplified benzonitrile derivatives are:



Compound	R1	R2	X	Formula
312431	CN	4-CN-Ph-CH2N(Bu)	2HCl	C ₃₄ H ₃₁ N ₅ ·2HCl
312433	CN	1-(EtOCO)-4-Pip-NH	2HCl	C ₃₀ H ₃₁ N ₅ O ₂ ·2HCl
312435	CN	4-[N(Me)2CO]-PhCH2O	HCl	C ₃₂ H ₂₈ N ₄ O ₂ ·HCl
312438	CN	4-CN-3-F-PhCH2O	HCl	C ₃₀ H ₂₁ FN ₄ O·HCl
312439	F	4-CN-PhCH2O	tosylate	C ₂₉ H ₂₂ FN ₃ O·C ₇ H ₆ O ₃ S
312441	CN	4-N3-PhCH2O	HCl	C ₂₉ H ₂₂ N ₆ O·HCl



312432: C30 H25 Cl N4 . 2HCl



312440: C31 H28 N4

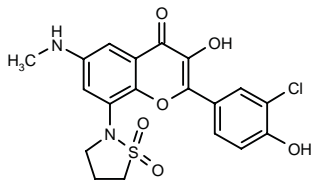
SOURCE – Abbott.

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1. Wang, W.-B. et al. (Abbott Laboratories Inc.) *Substd. phenyl farnesyltransferase inhibitors*. WO 0181316.

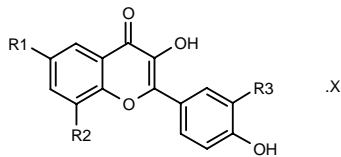
312566

2-(3-Chloro-4-hydroxyphenyl)-8-(1,1-dioxoisothiazolidin-2-yl)-3-hydroxy-6-(methylamino)-4*H*-1-benzopyran-4-one



C19 H17 Cl N2 O6 S; Mol wt: 436.8703

ACTION – An inhibitor of cyclin-dependent kinases (CDKs) with IC₅₀ values of 0.2 and 0.18 μM, respectively, against CDK2 and CDK4, and an oral LD₅₀ value of > 3000 mg/kg in acute toxicity tests in mice. Potentially useful for the treatment of cancer and other disorders related to cell proliferation such as inflammation, angiogenesis and angiostenosis. Other exemplified 3-hydroxychromen-4-one derivatives are:



Compound	R1	R2	R3	X	Formula
312567	Me	1,1-dioxo-2-isothiazolidinyl	H		C ₁₉ H ₁₇ NO ₆ S
312568	Me	1,1-dioxo-2-isothiazolidinyl	Cl		C ₁₉ H ₁₆ ClNO ₆ S
312569	N(Me)2	1,1-dioxo-2-isothiazolidinyl	Cl		C ₂₀ H ₁₉ ClN ₂ O ₆ S
312570	Me	1-Me-4-Pip	Cl		C ₂₂ H ₂₂ ClNO ₄
312571	Me	1-Me-4-Pyr ⁺	Cl	Br ⁻	C ₂₂ H ₁₇ BrClNO ₄

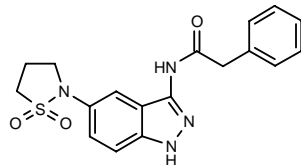
SOURCE – LG Chemical.

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1. Hong, C.Y. et al. (LG Chem Ltd.) *CDK inhibitors having 3-hydroxychromen-4-one structure*. WO 0183469.

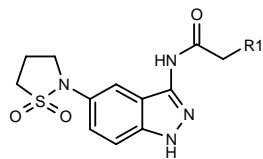
312846

N-[5-(1,1-Dioxoisothiazolidin-2-yl)-1*H*-indazol-3-yl]-2-phenylacetamide



C18 H18 N4 O3 S; Mol wt: 370.4312

ACTION – An inhibitor of cyclin-dependent kinases, particularly CDK2 and CDK4 (IC₅₀ < 0.05 and < 10 μM, respectively), potentially useful for the treatment of proliferative disorders such as cancer, inflammation, restenosis and angiogenesis. Other exemplified indazole derivatives include the following:



Compound	R1	Formula
312848	3-Cl-Ph	C ₁₈ H ₁₇ ClN ₄ O ₃ S
312850	4-OH-Ph	C ₁₈ H ₁₈ N ₄ O ₄ S
312851	4-(MeNH)-Ph	C ₁₉ H ₂₁ N ₅ O ₃ S
312853	1,3-benzodioxol-5-yl	C ₁₉ H ₁₈ N ₄ O ₅ S
312854	4-i-Pr-Ph	C ₂₁ H ₂₄ N ₄ O ₃ S
312856	4-(4-Pip)-Ph	C ₂₃ H ₂₇ N ₅ O ₃ S
312859	4-Ph-1-imidazolyl	C ₂₁ H ₂₀ N ₆ O ₃ S
312860	3,5-(MeO)2-Ph	C ₂₀ H ₂₂ N ₄ O ₅ S

SOURCE – LG Chemical.

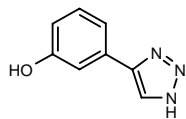
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1. Lee, J.H. et al. (LG Chem Ltd.) *Indazoles substd. with 1,1-dioxoisothiazolidine useful as inhibitors of cell proliferation.* WO 0185726.

ANGIOGENESIS INHIBITORS

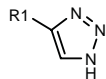
312196

3-(1*H*-1,2,3-Triazol-4-yl)phenol



C8 H7 N3 O; Mol wt: 161.1633

ACTION – A nonpeptide, reversible inhibitor of type 2 methionine aminopeptidase (MetAP2), expected to be useful for treating conditions mediated by angiogenesis such as cancer, hemangioma, proliferative retinopathy, rheumatoid arthritis, atherosclerotic neovascularization, psoriasis, ocular neovascularization and obesity. Other specifically claimed compounds include the following:



Compound	R1	Formula
312197	3-AcNH-Ph	C ₁₀ H ₁₀ N ₄ O
312198	2-Pyr	C ₇ H ₆ N ₄
312199	2-Me-Ph	C ₉ H ₉ N ₃
312200	4-Pyr	C ₇ H ₆ N ₄
312201	2-(4-Cl-PhS)-Ph	C ₁₄ H ₁₀ ClN ₃ S
312202	4-OH-Ph	C ₈ H ₇ N ₃ O
312203	Ph	C ₈ H ₇ N ₃

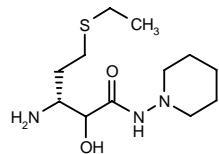
SOURCE – GlaxoSmithKline.

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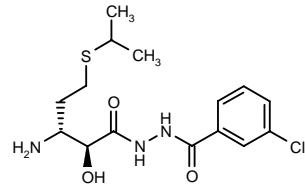
312222

3(*R*)-Amino-5-(ethylsulfanyl)-2-hydroxy-*N*-(1-piperidinyl)-pentanamide



C12 H25 N3 O2 S; Mol wt: 275.4145

ACTION – An inhibitor of type 2 methionine aminopeptidase (MetAP2), potentially useful as an anti-angiogenic agent. Another exemplified hydrazide compound is:



312227: C15 H22 Cl N3 O3 S

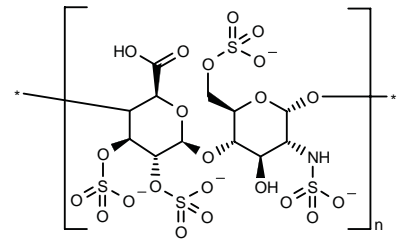
SOURCE – Abbott.

REFERENCES

1. Craig, R.A. et al. (Abbott Laboratories Inc.) *Hydrazide and alkoxyamide angiogenesis inhibitors.* WO 0179157.

312391

(1-*O*,4')-Poly[4-*O*-(2',3'-di-*O*-sulfonato- α -D-xylo-hexopyranuronosyl)-6-*O*-sulfonato-2-(sulfonatoamino)- α -D-glucopyranose]



(C12 H15 N O22 S4)n; Mol wt: 653.4995

ACTION – Sulfate derivative of the *Escherichia coli* K5 polysaccharide with high affinity for the fibroblast growth factor-2 (FGF-2) receptor (IC₅₀ = 10 ng/ml) and able to prevent FGF-2-mediated cell attachment, as well as FGF-2-induced cell proliferation in endothelial GM 7373 cells and in human umbilical vein endothelial cells. Moreover, compound showed potent antiangiogenic activity in the chick chorioallantoic membrane (CAM) assay. Potentially useful as an antiangiogenic agent for the treatment of cancer.

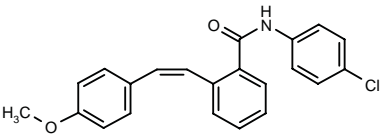
SOURCES – Università degli Studi di Bari, Bari (IT)
Università degli Studi di Brescia, Brescia (IT).

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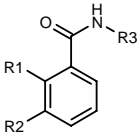
312533

N-(4-Chlorophenyl)-2-[(Z)-2-(4-methoxyphenyl)vinyl]-benzamide



C22 H18 Cl N O2; Mol wt: 363.8422

ACTION – Angiogenesis inhibitor that acts by inhibiting vascular endothelial growth factor receptor (VEGFR) and is indicated for the therapy of cancer. It exhibited IC₅₀ values of 0.2 µM for inhibition of VEGFR1 and VEGFR2. Other exemplified substituted benzoic acid amides are:



Compound	R1	R2	R3	Formula
312534	(Z)-4-MeO-PhCH=CH	H	3-quinolyl	C ₂₅ H ₂₀ N ₂ O ₂
312535	4-Pyr-CH2CH2	H	cyclohexyl-CH2	C ₂₁ H ₂₆ N ₂ O
312536	4-MeO-PhCH2CH2	H	3-quinolyl	C ₂₅ H ₂₂ N ₂ O ₂
312537	H	3-Pyr-ethynylene	4-Cl-Ph	C ₂₀ H ₁₃ ClN ₂ O
312538	(Z)-4-MeO-PhCH=CH	H	C7H15	C ₂₃ H ₂₉ NO ₂
312539	4-MeO-PhCH2CH2	H	4-Pr-Ph	C ₂₅ H ₂₇ NO ₂
312540	4-Pyr-CH2CH2	H	4-Pr-Ph	C ₂₃ H ₂₄ N ₂ O

SOURCE – Schering AG.

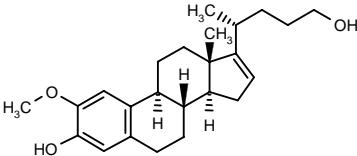
REFERENCES

1. Huth, A. et al. (Schering AG) *Substd. benzoic acid amides and uses thereof for the inhibition of angiogenesis*. DE 10021246, WO 0181311.

312918

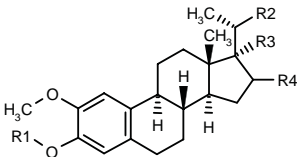
17-[4-Hydroxy-1 (R)-methylbutyl]-2-methoxyestra-1,3,5(10),16-tetraen-3-ol

2-Methoxy-19-norchola-1,3,5(10),16-tetraen-3,24-diol

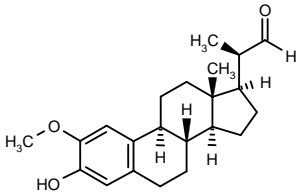


C24 H34 O3; Mol wt: 370.5296

ACTION – Antiproliferative and antiangiogenic agent, expected to be useful for the treatment of neoplastic diseases and for promoting wound healing, among others. Other compounds within this series of 2-substituted pregna-1,3,5(10)-triene and chola-1,3,5(10)-triene derivatives include the following:



Compound	R1	R2	R3	R4	Formula
312919	H	CH2OAc	bond		C ₂₄ H ₃₂ O ₄
312920	SO2NH2	CH2OH	H	H	C ₂₂ H ₃₁ NO ₅ S
312921	H	CH(OH)Me	H	H	C ₂₃ H ₃₂ O ₃
312924	SO2NH2	CH2OSO2NH2	bond		C ₂₂ H ₃₂ N ₂ O ₇ S ₂



312923: C22 H28 O3

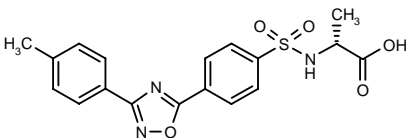
SOURCE – Research Institute for Medicine & Chemistry.

REFERENCES

1. Marsden, J.C. et al. (Research Institute for Medicine & Chemistry, Inc.) *2-Substd. pregna-1,3,5(10)-triene and chola-1,3,5(10)-triene derivs..* WO 0185755.

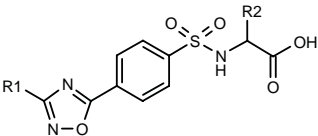
312994

N-[4-[3-(4-Methylphenyl)-1,2,4-oxadiazol-5-yl]phenyl-sulfonyl]-D-alanine



C18 H17 N3 O5 S; Mol wt: 387.4143

ACTION – A representative compound within a series of oxadiazoles that inhibits matrix metalloproteinase MMP-2 (gelatinase A; IC₅₀ = 30 nM) to a greater extent than MMP-8 (neutrophil collagenase; IC₅₀ > 1000 nM) or MMP-9 (gelatinase B; IC₅₀ = 470 nM). Potentially useful for the treatment of cancer, as demonstrated in a lung cancer model in mice. Other exemplified compounds are:



Compound	R1	R2	Isomer	Formula
312995	Ph	CH2Ph	R	C ₂₃ H ₁₉ N ₃ O ₅ S
312996	4-Cl-Ph	Me	R	C ₁₇ H ₁₄ ClN ₃ O ₅ S
312997	2-thienyl	i-Pr	R	C ₁₇ H ₁₇ N ₃ O ₅ S ₂
312998	4-F-Ph	Me	R	C ₁₇ H ₁₄ FN ₃ O ₅ S
312999	4-Et-Ph	CH2Ph	R	C ₂₅ H ₂₃ N ₃ O ₅ S
313000	4-Me-Ph	CH2Ph	S	C ₂₄ H ₂₁ N ₃ O ₅ S
313001	Ph	3-indolyl-CH2	R	C ₂₅ H ₂₀ N ₄ O ₅ S
313002	Ph	Me	R	C ₁₇ H ₁₅ N ₃ O ₅ S

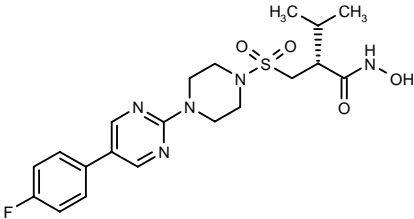
SOURCE – Shionogi.

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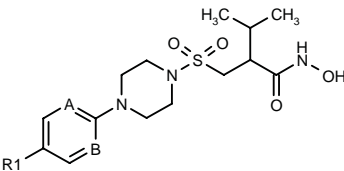
313229

2(R)-[4-[5-(4-Fluorophenyl)pyrimidin-2-yl]piperazin-1-ylsulfonylmethyl]-3-methylbutyroxamic acid



C20 H26 F N5 O4 S; Mol wt: 451.5204

ACTION – An inhibitor of matrix metalloproteinases (MMPs) including stromelysin, collagenase, gelatinase or ADAM and ADAM-TS enzymes. Potentially useful for the treatment of cancer, transplant rejection, psoriasis, atopic dermatitis, rhinitis, eczema, systemic lupus erythematosus, cystic fibrosis, arthritis, osteoporosis, Crohn’s disease, ulcerative colitis, multiple sclerosis, bacterial infections, asthma, chronic obstructive pulmonary disease, ocular diseases, etc. Other specifically claimed hydroxamic acid derivatives are:



Compound	R1	A	B	Isomer	Formula
313231	2-furyl	CH	CH		C ₂₀ H ₂₇ N ₃ O ₅ S
313235	4-Cl-Ph	N	CH	R	C ₂₁ H ₂₇ ClN ₄ O ₄ S
313237	4-CF3-Ph	N	N	R	C ₂₁ H ₂₆ F ₃ N ₅ O ₄ S

SOURCE – Celltech Group.

REFERENCES

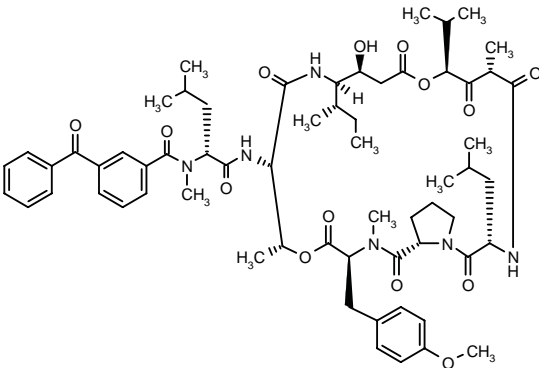
1. Hannah, D.R. et al. (Celltech Group plc) *Hydroxamic acid derivs*. WO 0187870.

OTHER ONCOLYTIC DRUGS

311979

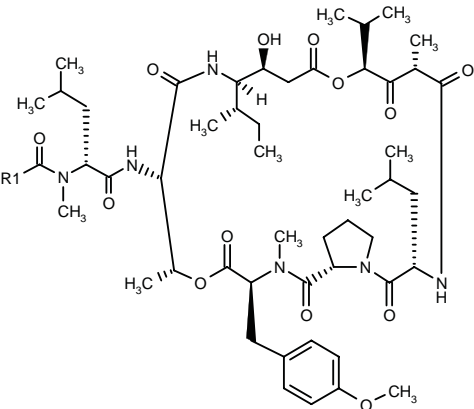
(3*S*,6*S*,8*S*,12*S*,13*R*,16*S*,17*R*,20*S*,23*S*)-16-[*N*-(3-Benzoylbenzoyl)-*N*-methyl-D-leucylamino]-12-hydroxy-3-isobutyl-8-isopropyl-20-(4-methoxybenzyl)-6,17,21-trimethyl-13-[1(*S*)-methylpropyl]-9,18-dioxo-1,4,14,21-tetraazabicyclo[21.3.0]hexacosane-2,5,7,10,15,19,22-heptaone

N-(3-Benzoylbenzoyl)-*N*-methyl-D-leucyl-L-threonyl-(3*S*,4*R*,5*S*)-4-amino-3-hydroxy-5-methylheptanoyl-(2*S*,4*S*)-4-hydroxy-2,5-dimethyl-3-oxohexanoyl-L-leucyl-L-prolyl-*N*,*O*-dimethyl-L-tyrosine *O*-2.2-*C*-1.7-lactone



C63 H86 N6 O14; Mol wt: 1151.4000

ACTION – Potential antitumor agent, a macrocyclic peptidomimetic compound reported to have proapoptotic and protein biosynthesis-inhibitory activity. Compound was shown to inhibit protein biosynthesis in a cell-free translation assay, with an IC₅₀ of 4.0 μM. When tested against the NCI 60 tumor cell line panel, it gave 50% growth inhibition (GI₅₀) and total growth inhibition (TGI) values of 3.0 nM and 0.35 μM, respectively, while having a lethal concentration LC₅₀ of 15 μM. Other exemplified compounds from this series of tamandarin and didemnin analogues are:



Compound	R1	Formula
311981	3-(PhCO)-PhCONHCH2	C ₆₅ H ₈₉ N ₇ O ₁₅
311982	3-(PhCO)-PhCONH(CH2)5	C ₆₉ H ₉₇ N ₇ O ₁₅
311983	3-(PhCO)-PhCONH(CH2)5CONH(CH2)5	C ₇₅ H ₁₀₈ N ₈ O ₁₆

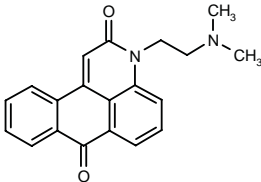
SOURCE – University of Pennsylvania, Philadelphia, PA (US).

REFERENCES

1. Joullie, M.M. et al. (University of Pennsylvania) *Tamandarin and didemnin analogs and methods of making and using them*. WO 0176616.

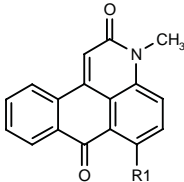
312065

3-[2-(Dimethylamino)ethyl]-3,7-dihydro-2*H*-dibenzo[*f,i*]-isoquinoline-2,7-dione



C20 H18 N2 O2; Mol wt: 318.3742

ACTION – Antitumor agent with IC₅₀ values of 0.60, 1.60 and 0.31 µg/ml for inhibition of the proliferation of human breast cancer MCF-7 and MDA-MB-231 and human colon cancer HCT 116 cells, respectively. Other exemplified anthrapyridones include the following:



Compound	R1	Formula
312066	H	C ₁₇ H ₁₁ NO ₂
312067	OH	C ₁₇ H ₁₁ NO ₃

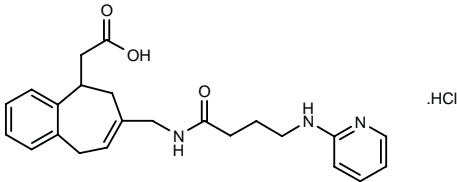
SOURCE – Nippon Kayaku.

REFERENCES

1. Yokumoto, H. et al. (Nippon Kayaku Co., Ltd.) *Novel anthrapyridones medicinal agents*. JP 2001288091.

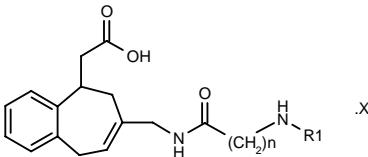
312184

2-[7-[4-(Pyridin-2-ylamino)butyramidomethyl]-6,9-dihydro-5*H*-benzocyclohepten-5-yl]acetic acid hydrochloride

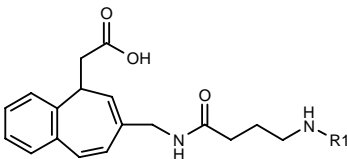


C23 H27 N3 O3 . HCl; Mol wt: 429.9452

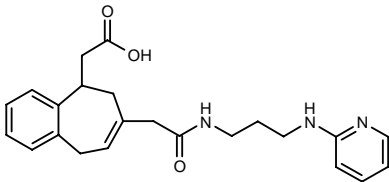
ACTION – Vitronectin α_vβ₃ and/or α_vβ₅ receptor antagonist with selectivity over integrin αIIbβ₃ receptors. Potentially useful for the treatment of cancer, as well as cardiovascular diseases, inflammation, osteoporosis, rheumatoid arthritis, psoriasis and retinopathies. Other specifically claimed compounds are:



Compound	R1	n	X	Formula
312185	2-Pyr	4	HCl	C ₂₄ H ₂₉ N ₃ O ₃ .HCl
312190	4,5-dihydro-2-imidazolyl	3	HCl	C ₂₁ H ₂₈ N ₄ O ₃ .HCl
312193	2-benzimidazolyl	3		C ₂₅ H ₂₈ N ₄ O ₃
312194	3,4,5,6-tetrahydro-2-pyrimidinyl	3	HCl	C ₂₂ H ₃₀ N ₄ O ₃ .HCl
312195	5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl	3	HCl	C ₂₆ H ₃₂ N ₄ O ₃ .HCl



Compound	R1	Formula
312191	2-Pyr	C ₂₃ H ₂₈ N ₃ O ₃
312192	2-benzimidazolyl	C ₂₅ H ₂₈ N ₄ O ₃



312188: C23 H27 N3 O3

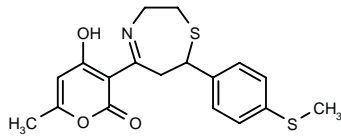
SOURCE – ADIR.

REFERENCES

1. Casara, P. et al. (ADIR et Cie.) *Method and compsns. containing same*. FR 2806082, WO 0179172.

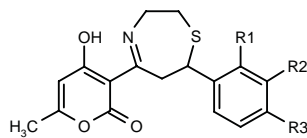
312278

4-Hydroxy-6-methyl-3-[7-[4-(methylsulfanyl)phenyl]-2,3,6,7-tetrahydro-1,4-thiazepin-5-yl]-2H-pyran-2-one

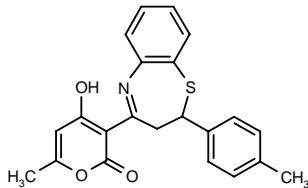


C18 H19 N O3 S2; Mol wt: 361.4841

ACTION – Agent that activates caspases and induces apoptosis, proven effective in activating the caspase cascade in human breast cancer T-47D and ZR-75-1 cells (EC₅₀ = 345 and 163 nM, respectively). Potentially useful for the treatment of conditions involving uncontrolled growth of abnormal cells such as cancer. Other exemplified compounds are:



Compound	R1	R2	R3	Formula
312282	H	OMe	H	C ₁₈ H ₁₉ NO ₄ S
312284	Br	H	H	C ₁₇ H ₁₆ BrNO ₃ S
312286	H	Cl	Cl	C ₁₇ H ₁₅ Cl ₂ NO ₃ S



312287: C22 H19 N O3 S

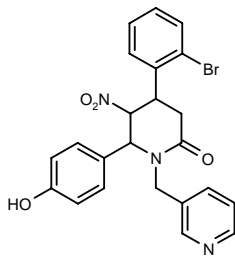
SOURCE – Cytovia.

REFERENCES

1. Cai, S.X. et al. (Cytovia, Inc.) *Substd. 1,4-thiazepine and analogs as activators of caspases and inducers of apoptosis and the use thereof.* WO 0179187.

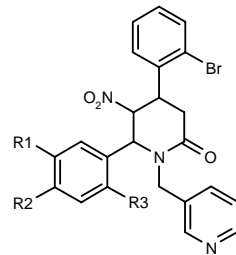
312825

(±)-4-(2-Bromophenyl)-6-(4-hydroxyphenyl)-5-nitro-1-(pyridin-3-ylmethyl)piperidin-2-one



C23 H20 Br N3 O4; Mol wt: 482.3320

ACTION – Antitumor agent shown to inhibit the proliferation of human colon cancer DLD-1 cells with an IC₅₀ of 18 μM. *In vivo*, it reduced the volume of DLD-1 xenografts subcutaneously transplanted into mice with a T/C value of 47% following i.p. administration at a dose of 50 mg/kg b.i.d. for 10 days. Other exemplified 5-nitropiperidin-2-one derivatives include the following:



Compound	R1	R2	R3	Isomer	Formula
312826	OH	OH	H	racemic	C ₂₃ H ₂₀ BrN ₃ O ₅
312827	OH	OH	H	(+)	C ₂₃ H ₂₀ BrN ₃ O ₅
312828	OH	OH	H	(-)	C ₂₃ H ₂₀ BrN ₃ O ₅
312829	OMe	H	OMe		C ₂₅ H ₂₄ BrN ₃ O ₅
312830	H	H	OEt		C ₂₅ H ₂₄ BrN ₃ O ₄

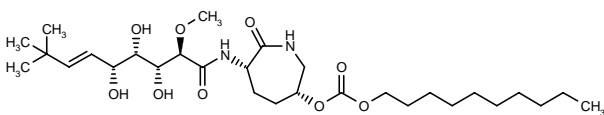
SOURCES – Kyowa Hakko; Lilly.

REFERENCES

1. Kanda, Y. et al. (Eli Lilly and Company;Kyowa Hakko Kogyo Co., Ltd.) *2-Piperidone cpds. for the treatment of cancer.* WO 0185716.

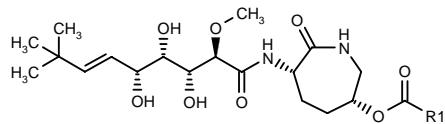
313106

Carbonic acid decyl 7-oxo-6(*S*)-[3(*R*),4(*S*),5(*R*)-trihydroxy-2(*R*)-methoxy-8,8-dimethyl-6(*E*)-nonenamido]azepan-3(*R*)-yl diester



C29 H52 N2 O9; Mol wt: 572.7348

ACTION – Antitumor agent with IC₅₀ values of 0.21, 0.57 and 0.53 μM, respectively, against human breast cancer MDA-MB-435, human lung cancer H1299 and human colon carcinoma HCT 116 cells. Compound also demonstrated *in vivo* activity in athymic nude mice bearing MDA-MB-435 xenografts at a dose of 3.3 μmol/kg i.p. 3 times per week for 3 weeks, or human non-small cell lung carcinoma A549 xenografts at a dose of 30 μmol/kg i.p. 5 times per week for 2 weeks. Other compounds within this series of caprolactam-containing carbonates and ethers are:



Compound	R1	Formula
313109	OC5H11	C ₂₄ H ₄₂ N ₂ O ₉
313112	OCH2CH2Ph	C ₂₇ H ₄₀ N ₂ O ₉
313113	OCH2Ph	C ₂₆ H ₃₈ N ₂ O ₉
313114	t-BuCH2O	C ₂₄ H ₄₂ N ₂ O ₉
313115	cyclohexyl-O	C ₂₅ H ₄₂ N ₂ O ₉
313116	CH2OC11H23	C ₃₁ H ₅₆ N ₂ O ₉

SOURCE – Novartis.

REFERENCES

1. Kinder, F.R. Jr. et al. (Novartis AG;Novartis-Erfindungen VmbH) *Substd. caprolactam carbonates and ethers and their use as anti-tumor agents.* WO 0185697.

BR96-CAMPTOTHECIN

314552

Immunoconjugate consisting of the monoclonal antibody BR96 attached to the hydroxyl group at C-20 of camptothecin through the cathepsin B-cleavable linker 4-[N-(6-succinimidohexanoyl)-DL-phenylalanyl-DL-lysylamino]benzyloxycarbonyl

ACTION – Immunoconjugate of camptothecin in which the drug is attached to the tumor-recognizing antibody BR96 via a cathepsin B-cleavable linker. The immunoconjugate showed comparable cytotoxicity to camptothecin in human lung adenocarcinoma L2987 cells (IC₅₀ = 0.1 and 0.4 μM, respectively) and is expected to be less toxic than the parent drug to normal tissue *in vivo*.

SOURCE – Bristol-Myers Squibb.

REFERENCES

1. Firestone, R.A. and Dubowchik, G.M. (Bristol-Myers Squibb Co.) *Lysosomal enzyme-cleavable antitumor drug conjugates.* EP 0624377.

2. Walker, M.A. et al. *Synthesis of an immunoconjugate of camptothecin.* Bioorg Med Chem Lett 2002, 12(2): 217.

DX-306

311715

L-Aspartyl-L-tryptophyl-L-valyl-L-cysteinyl-L-glutamyl-L-tyrosyl-L-phenylalanyl-L-lysyl-L-asparaginyl-L-glutaminy-L-tryptophyl-L-phenylalanyl-L-cysteinyl-L-asparaginyl-L-valyl-L-leucine

304A-12-H12

C99 H132 N22 O25 S2; Mol wt: 2094.3930

ACTION – Peptide with affinity for carcinoembryonic antigen (CEA) that displays K_D values of 3.7 and 0.24 μM against CEA and the truncated CEA H6NA3, respectively. Potentially useful for the detection and treatment of cancer, particularly colon, breast, lung, cervical, ovarian, stomach, bladder, pancreas and esophageal cancers.

SOURCE – Dyax.

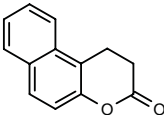
REFERENCES

1. Rondon, I.J. and Ladner, R.C. (Dyax Corp.) *Binding peptides for carcinoembryonic antigen (CEA).* WO 0174849.

SPLITOMICIN

313483

1,2-Dihydro-3*H*-benzo[*f*]-1-benzopyran-3-one



C13 H10 O2; Mol wt: 198.2200

ACTION – Potential antineoplastic agent, a selective inhibitor of the silence information regulator protein Sir2p proven to block the histone deacetylase activity of the Sir2p protein (IC₅₀ = 60 μM).

SOURCE – Fred Hutchinson Cancer Research Center, Seattle, WA (US).

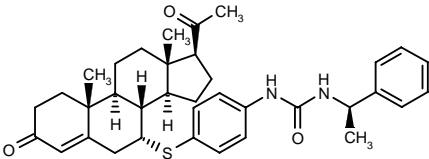
REFERENCES

1. Bedalov, A. et al. *Identification of a small molecule inhibitor of Sir2p.* Proc Natl Acad Sci USA 2001, 98(26): 15113.

MODULATORS OF THE THERAPEUTIC ACTIVITY OF ANTINEOPLASTIC AGENTS

313613

N-[4-(3,20-Dioxopregn-4-en-7α-ylsulfanyl)phenyl]-N'-[1(*R*)-phenylethyl]urea



C36 H44 N2 O3 S; Mol wt: 584.8206

ACTION – Multidrug resistance modulator, a C-7 progesterone analogue able to strongly inhibit the P-glycoprotein efflux pump. It showed 60-fold higher potency than progesterone for restoring doxorubicin accumulation in MDR1-transduced breast cancer cells. Compound did not bind to progesterone receptors, indicating potentially reduced *in vivo* toxicity.

SOURCE – Georgetown University, Washington, DC (US).

REFERENCES

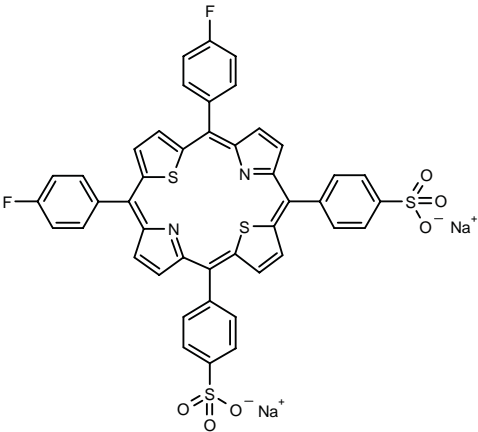
1. Clarke, R. et al. (Georgetown University) *Progesterone analogs to reverse multidrug resistance.* WO 9700683.

2. Leonessa, F. et al. *C-7 analogues of progesterone as potent inhibitors of the P-glycoprotein efflux pump.* J Med Chem 2002, 45(2): 390.

PHOTODYNAMIC THERAPY

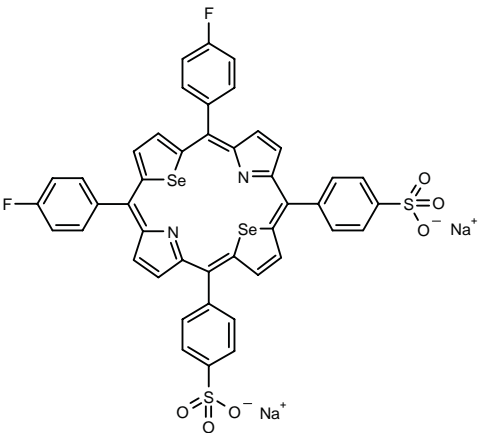
313615

5,20-(4-Fluorophenyl)-10,15-bis(4-sulfophenyl)-21,23-dithiaporphyrin disodium salt



C44 H24 F2 N2 Na2 O6 S4; Mol wt: 888.9216

ACTION – Core-modified porphyrin photosensitizer for photodynamic therapy, able to absorb longer wavelengths, with phototoxicity *in vitro* against murine colon carcinoma Colo-26 cells (EC₅₀ = 1.6 μM for cell killing with 4 J/cm² of light). Compound was not toxic in mice and was well tolerated at a dose of 10 mg/kg i.v. In mice bearing Colo-26 carcinoma, it was found to accumulate in tumors rather than in liver, kidney, lung, heart and spleen; a dose of 0.125 mg/kg followed by irradiation with 135 J cm² of red light (694 nm) showed efficacy comparable to that of Photofrin (porfimer sodium) in prolonging survival in mice. Another related compound is:



313616: C44 H24 F2 N2 Na2 O6 S2 Se2

SOURCES – State University of New York, Albany, NY (US); University of Rochester Medical Center, Rochester, NY (US); Roswell Park Cancer Institute, Buffalo, NY (US).

REFERENCES

1. Hilmey, D.G. et al. *Water-soluble, core-modified porphyrins as novel longer-wavelength-absorbing sensitizers for photodynamic therapy. II. Effects of core heteroatoms and meso-substituents on biological activity.* J Med Chem 2002, 45(2): 449.

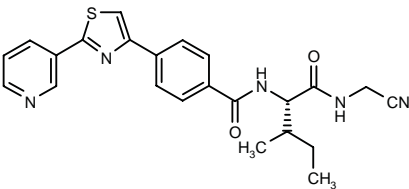
METABOLIC DRUGS

TREATMENT OF BONE DISEASES

310217

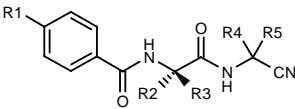
N-[1(*S*)-[*N*-(Cyanomethyl)carbamoyl]-2-methylbutyl]-4-[2-(3-pyridyl)thiazol-4-yl]benzamide

*N*¹-(Cyanomethyl)-*N*²-[4-[2-(3-pyridyl)thiazol-4-yl]-benzoyl]-*L*-isoleucinamide

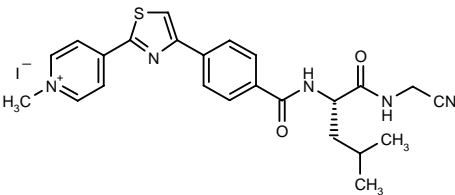


C23 H23 N5 O2 S; Mol wt: 433.5337

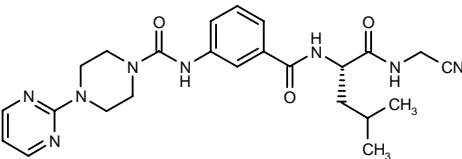
ACTION – Agent with the ability to inhibit cysteine proteases such as cathepsins B, K, L and/or S, considered to have potential for the treatment of postmenopausal osteoporosis. Other exemplified *N*-cyanomethyl amides are:



Compound	R1	R2	R3	R4	R5	Formula
310230	2-[4-(<i>t</i> -BuOCO)-1-Piz]-4-thiazolyl	<i>i</i> -Bu	H	H	H	C ₂₇ H ₃₀ N ₆ O ₄ S
310234	4-(1-Piz-CH2)-2-thiazolyl-NH	<i>i</i> -Bu	H	H	H	C ₂₃ H ₃₁ N ₇ O ₂ S
310236	2-(4-CO2H-1-Piz)-4-thiazolyl-CH2O	-(CH2)5-		H	H	C ₂₈ H ₃₀ N ₆ O ₅ S
310237	2-(1-Piz-CH2)-4-thiazolyl	<i>i</i> -Bu	H	-CH2CH2-		C ₂₈ H ₃₂ N ₆ O ₂ S



310226: C24 H26 I N5 O2 S

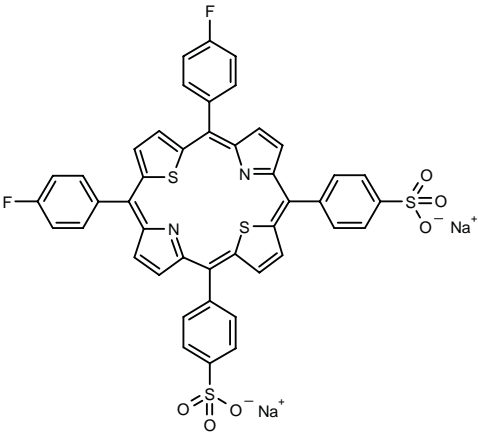


310235: C24 H30 N8 O3

PHOTODYNAMIC THERAPY

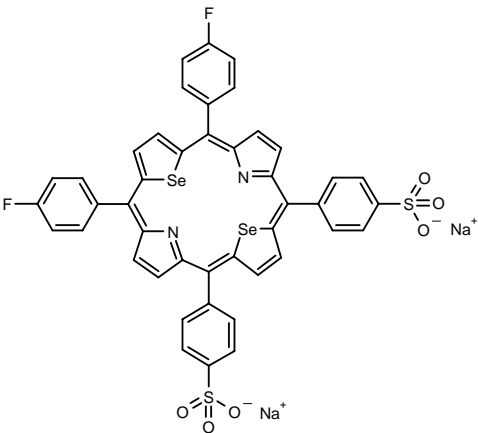
313615

5,20-(4-Fluorophenyl)-10,15-bis(4-sulfophenyl)-21,23-dithiaporphyrin disodium salt



C44 H24 F2 N2 Na2 O6 S4; Mol wt: 888.9216

ACTION – Core-modified porphyrin photosensitizer for photodynamic therapy, able to absorb longer wavelengths, with phototoxicity *in vitro* against murine colon carcinoma Colo-26 cells (EC₅₀ = 1.6 μM for cell killing with 4 J/cm² of light). Compound was not toxic in mice and was well tolerated at a dose of 10 mg/kg i.v. In mice bearing Colo-26 carcinoma, it was found to accumulate in tumors rather than in liver, kidney, lung, heart and spleen; a dose of 0.125 mg/kg followed by irradiation with 135 J cm² of red light (694 nm) showed efficacy comparable to that of Photofrin (porfimer sodium) in prolonging survival in mice. Another related compound is:



313616: C44 H24 F2 N2 Na2 O6 S2 Se2

SOURCES – State University of New York, Albany, NY (US); University of Rochester Medical Center, Rochester, NY (US); Roswell Park Cancer Institute, Buffalo, NY (US).

REFERENCES

1. Hilmey, D.G. et al. *Water-soluble, core-modified porphyrins as novel longer-wavelength-absorbing sensitizers for photodynamic therapy. II. Effects of core heteroatoms and meso-substituents on biological activity.* J Med Chem 2002, 45(2): 449.

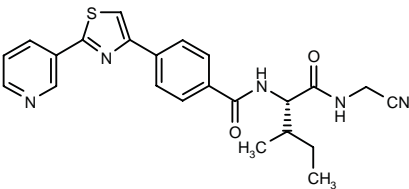
METABOLIC DRUGS

TREATMENT OF BONE DISEASES

310217

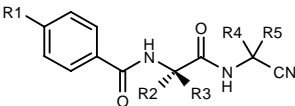
N-[1(*S*)-[*N*-(Cyanomethyl)carbamoyl]-2-methylbutyl]-4-[2-(3-pyridyl)thiazol-4-yl]benzamide

*N*¹-(Cyanomethyl)-*N*²-[4-[2-(3-pyridyl)thiazol-4-yl]-benzoyl]-*L*-isoleucinamide

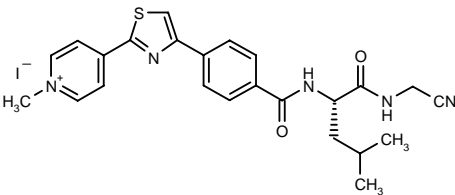


C23 H23 N5 O2 S; Mol wt: 433.5337

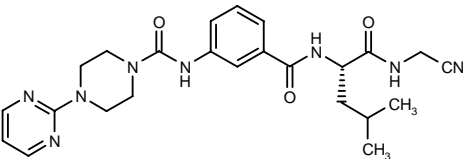
ACTION – Agent with the ability to inhibit cysteine proteases such as cathepsins B, K, L and/or S, considered to have potential for the treatment of postmenopausal osteoporosis. Other exemplified *N*-cyanomethyl amides are:



Compound	R1	R2	R3	R4	R5	Formula
310230	2-[4-(<i>t</i> -BuOCO)-1-Piz]-4-thiazolyl	<i>i</i> -Bu	H	H	H	C ₂₇ H ₃₀ N ₆ O ₄ S
310234	4-(1-Piz-CH2)-2-thiazolyl-NH	<i>i</i> -Bu	H	H	H	C ₂₃ H ₃₁ N ₇ O ₂ S
310236	2-(4-CO2H-1-Piz)-4-thiazolyl-CH2O	-(CH2)5-		H	H	C ₂₈ H ₃₀ N ₆ O ₅ S
310237	2-(1-Piz-CH2)-4-thiazolyl	<i>i</i> -Bu	H	-CH2CH2-		C ₂₈ H ₃₂ N ₆ O ₂ S



310226: C24 H26 I N5 O2 S



310235: C24 H30 N8 O3

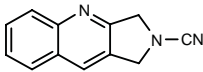
SOURCE – Celera Genomics.

REFERENCES

1. Palmer, J.T. et al. (Celera Genomics) *Novel cpds. and compsns. as protease inhibitors*. WO 0168645.

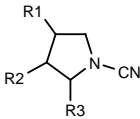
311986

2,3-Dihydro-1*H*-pyrrolo[3,4-*b*]quinoline-2-carbonitrile

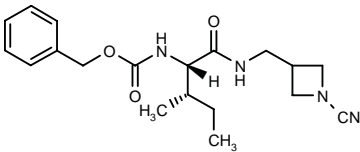


C12 H9 N3; Mol wt: 195.2241

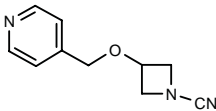
ACTION – An inhibitor of cysteine proteases such as cathepsins K and L. By virtue of its activity as an inhibitor of bone loss, compound is expected to be useful for the prevention and treatment of bone fractures and osteoporosis. Other specifically claimed compounds include the following:



Compound	R1	R2	R3	Formula
311987	H	H	CH2NHCOPh	C ₁₃ H ₁₅ N ₃ O
311988	H	CO2Me	H	C ₇ H ₁₀ N ₂ O ₂
311990	H	4-Ph-PhCONH	H	C ₁₈ H ₁₇ N ₃ O
311991	H	CH2OCH2Ph	H	C ₁₃ H ₁₆ N ₂ O
311993	OCH2Ph	NHSO2Ph	H	C ₁₈ H ₁₈ N ₃ O ₃ S



311989: C19 H26 N4 O3



311992: C10 H11 N3 O

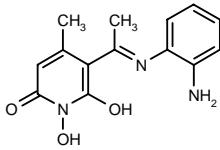
SOURCES – Banyu; Celera Genomics; Merck Frosst.

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312813

5-[1-(2-Aminophenylimino)ethyl]-1,6-dihydroxy-4-methylpyridin-2(1*H*)-one



C14 H15 N3 O3; Mol wt: 273.2905

ACTION – A representative compound from a series of 6-hydroxypyridin-2-one derivatives with calcitonin receptor-agonist activity. *In vitro*, the compound was able to increase the concentration of cAMP in human breast cancer T47-D cells and rat osteosarcoma UMR106-66 cells. It also demonstrated *in vivo* activity, lowering the concentration of serum calcium at 100 mg/kg i.p. in rats. Potentially useful for the treatment of osteoporosis, Paget's disease, hyperparathyroidism, osteomalacia and hypercalcemia.

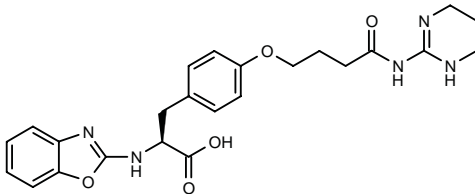
SOURCE – Suntory.

REFERENCES

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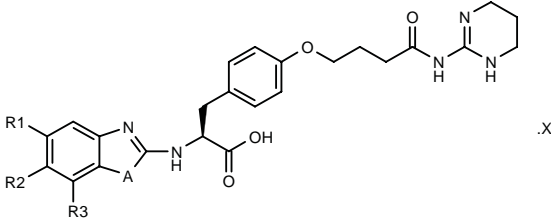
312818

N-(2-Benzoxazolyl)-4-*O*-[3-[*N*-(1,4,5,6-tetrahydropyrimidin-2-yl)carbamoyl]propyl]-L-tyrosine

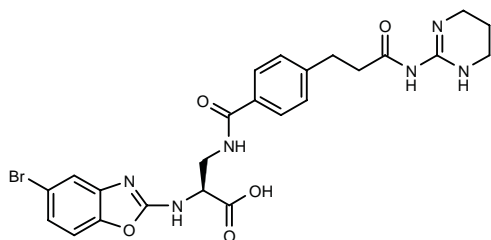


C24 H27 N5 O5; Mol wt: 465.5073

ACTION – A vitronectin ($\alpha_v\beta_3$) receptor antagonist (IC₅₀ = 5 nM), potentially useful for the treatment of osteoporosis, cancer and other vitronectin-mediated disorders including inflammation, cardiovascular disorders, restenosis, arteriosclerosis, nephropathies and retinopathies. Other exemplified compounds are:



Compound	R1	R2	R3	A	X	Formula
312819	H	H	H	S		C ₂₄ H ₂₇ N ₅ O ₄ S
312821	H	H	Cl	O	CF3CO2H	C ₂₄ H ₂₆ ClN ₅ O ₅ ·C ₂ HF ₃ O ₂
312822	-CH=CHCH=CH-	H	O			C ₂₈ H ₂₈ N ₅ O ₅
312823	Ph	H	H	O		C ₃₀ H ₃₁ N ₅ O ₅
312824	SO2N(Me)Ph	H	H	O		C ₃₁ H ₃₄ N ₆ O ₇ S



312820: C₂₄ H₂₅ Br N₆ O₅

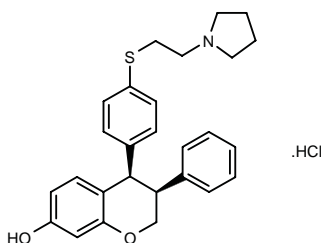
SOURCE – Aventis Pharma.

REFERENCES

1. Demassey, J. et al. (Aventis Pharma SA) *Novel vitronectin receptor antagonists*. WO 0185729.

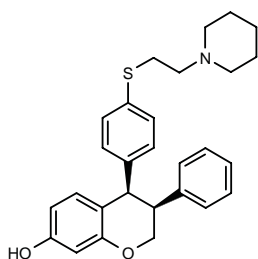
314270

(±)-*cis*-3-Phenyl-4-[4-[2-(1-pyrrolidiny)ethylsulfanyl]-phenyl]-3,4-dihydro-2*H*-1-benzopyran-7-ol hydrochloride



C₂₇ H₂₉ N O₂ S . HCl; Mol wt: 468.0580

ACTION – Nonsteroidal high-affinity estrogen receptor ligand (IC₅₀ = 6.5 nM) with partial agonist activity *in vitro* in the Ishikawa line of human endometrial adenocarcinoma cells (EC₅₀ = 0.5 nM and E_{max} = 5% relative to moxestrol). Potentially useful for the treatment of postmenopausal osteoporosis. Another related compound is:



314269: C₂₈ H₃₁ N O₂ S

SOURCE – Novo Nordisk.

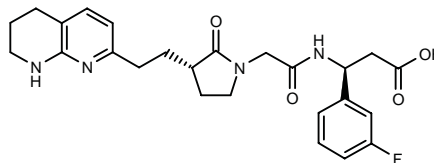
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1. Jacobsen, P. et al. (Novo Nordisk A/S) *Novel cis-3,4-chroman derivs. useful in the prevention or treatment of estrogen related diseases or syndromes*. EP 0937061, JP 2001502709, US 5919817, WO 9818777.

2. Christiansen, L.B. et al. *Synthesis and biological evaluation of novel thio-substituted chromanes as high-affinity partial agonists for the estrogen receptor*. Bioorg Med Chem Lett 2002, 12(1): 17.

314271

3-(*S*)-(3-Fluorophenyl)-3-[2-[2-oxo-3(*S*)-[2-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)ethyl]pyrrolidin-1-yl]-acetamido]propionic acid



C₂₅ H₂₉ F N₄ O₄; Mol wt: 468.5261

ACTION – Nonpeptide integrin $\alpha_v\beta_3$ antagonist with nanomolar affinity for human recombinant $\alpha_v\beta_3$ receptors (IC₅₀ = 1.8 nM) and high selectivity over fibrinogen receptors (IC₅₀ > 1 μ M). Compound exhibited a favorable pharmacokinetic profile in dogs, with an oral bioavailability of 44%. Potentially useful for the treatment of osteoporosis.

SOURCE – Merck & Co.

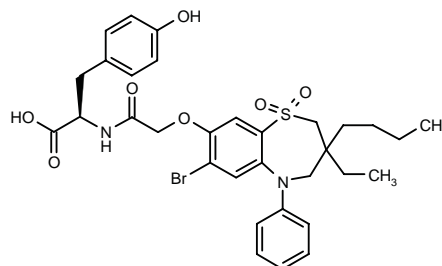
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1. Coleman, P.J. et al. *Non-peptide alphavbeta3 antagonists. Part 3: Identification of potent RGD mimetics incorporating novel β -amino acids as aspartic acid replacements*. Bioorg Med Chem Lett 2002, 12(1): 31.

TREATMENT OF LIPOPROTEIN DISORDERS

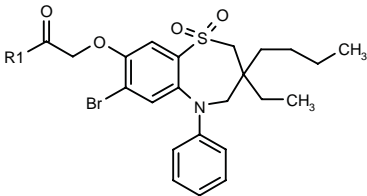
310177

N-[2-(7-Bromo-3-butyl-3-ethyl-1,1-dioxo-5-phenyl-2,3,4,5-tetrahydro-1,5-benzothiazepin-8-yloxy)acetyl]-D-tyrosine

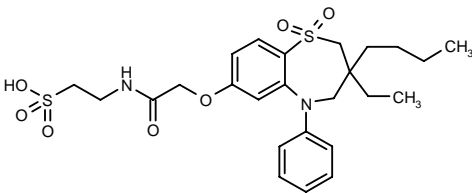


C₃₂ H₃₇ Br N₂ O₇ S; Mol wt: 673.6213

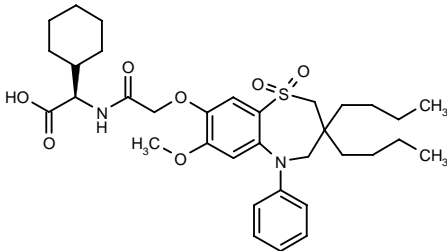
ACTION – An inhibitor of ileal bile acid transport with potential in the treatment of hyperlipidemia and hypercholesterolemia, either alone or administered with an HMG-CoA reductase inhibitor. Other exemplified 1,5-benzothiazepines are:



Compound	R1	Formula
310179	-Gly-OH	C ₂₅ H ₃₁ BrN ₂ O ₆ S
310181	-L-Phe-OH	C ₃₂ H ₃₇ BrN ₂ O ₆ S
310182	-D-Ala-OH	C ₂₆ H ₃₃ BrN ₂ O ₆ S
310183	-L-Val-OH	C ₂₈ H ₃₇ BrN ₂ O ₆ S
310184	-L-Ile-OH	C ₂₉ H ₃₉ BrN ₂ O ₆ S
310186	-L-Thr-OH	C ₂₇ H ₃₅ BrN ₂ O ₇ S



310180: C₂₅ H₃₄ N₂ O₇ S₂



310185: C₂₅ H₃₄ N₂ O₇ S₂

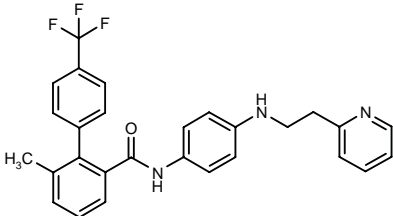
SOURCE – AstraZeneca.

REFERENCES

1. Starke, I. et al. (AstraZeneca AB;AstraZeneca plc) 1,5-Benzothiazepines and their use as hypolipidaemics. WO 0166533.

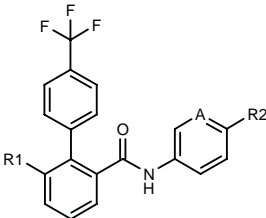
311967

6-Methyl-*N*-[4-[2-(2-pyridyl)ethylamino]phenyl]-4'-(tri-fluoromethyl)biphenyl-2-carboxamide



C₂₈ H₂₄ F₃ N₃ O; Mol wt: 475.5116

ACTION – Agent that inhibits the secretion of microsomal triglyceride transfer protein (MTP) and apolipoprotein B (apo B), with IC₅₀ values of 1 and 90 nM, respectively, when tested *in vitro* in apo B and MTP assays. It also demonstrated plasma triglyceride- and cholesterol-lowering activity following oral administration to rats at a dose of 5 mg/kg. Potentially useful for the treatment of hypertriglyceridemia and hypercholesterolemia, as well as disorders associated therewith such as cardiovascular disorders including cardiac ischemia, atherosclerosis, obesity, pancreatitis and diabetes. Other exemplified aryl carboxamide derivatives are:



Compound	R1	R2	A	Formula
311968	Me	2-Pyr-OCH ₂ CH ₂	CH	C ₂₈ H ₂₃ F ₃ N ₂ O ₂
311970	Me	2-Pyr-CH ₂ CH ₂ O	CH	C ₂₈ H ₂₃ F ₃ N ₂ O ₂
311971	H	2-Pyr-CH ₂ CH ₂ NH	N	C ₂₈ H ₂₁ F ₃ N ₄ O
311972	H	CH ₂ CH ₂ NHSO ₂ Ph	CH	C ₂₈ H ₂₃ F ₃ N ₂ O ₃ S
311973	Me	NHCH ₂ CH ₂ NHCO ₂ Me	CH	C ₂₅ H ₂₄ F ₃ N ₃ O ₃
311974	Me	OCH ₂ CH ₂ NHCO ₂ Me	CH	C ₂₅ H ₂₃ F ₃ N ₂ O ₄
311975	H	NHCH ₂ CH ₂ NHCO ₂ Me	N	C ₂₃ H ₂₁ F ₃ N ₄ O ₃

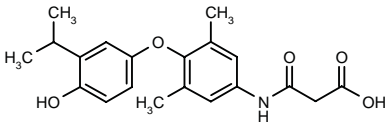
SOURCE – Novartis.

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313154

N-[4-(4-Hydroxy-3-isopropylphenoxy)-3,5-dimethyl-phenyl]malonic acid



C₂₀ H₂₃ N O₅; Mol wt: 357.4037

ACTION – A representative compound from a series of malonic acid derivatives with lipid-lowering activity. This compound decreased blood non-HDL cholesterol and triglyceride levels in dogs following oral administration, with ED₂₀ values of 4.22 and 46.0 nmol/kg, respectively. It also displayed a dose-dependent protective effect against lipopolysaccharide- and D-galactosamine-induced hepatitis when administered orally to rats at doses of 30 nmol/kg and 300 nmol/kg, and caused no deaths in acute toxicity tests in rats (3000 nmol/kg/day p.o. for 2 weeks).

SOURCE – Kissei.

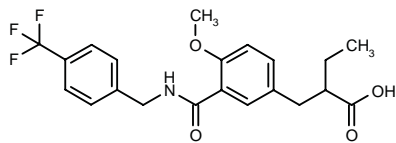
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KCL-1998001079*

298465

(±)-2-[4-Methoxy-3-[N-[4-(trifluoromethyl)benzyl]-carbamoyl]benzyl]butyric acid



C21 H22 F3 N O4; Mol wt: 409.4018

ACTION – Peroxisome proliferator-activated receptor (PPAR) activator with high selectivity for PPAR α over PPAR γ receptors (EC₅₀ = 0.040 and 0.40 μ M, respectively, in a transactivation assay). Potentially useful for the treatment of lipoprotein disorders.

SOURCE – Kyorin.

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*Identified compound **298465** Drug Data Rep 2001, 023(05): 0518.

NIACIN/LOVASTATIN New combination

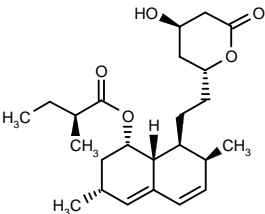
276281

Combination of extended-release niacin and immediate-release lovastatin

Lovastatin

090077

2-Methylbutanoic acid [1S-[1 α (R*),3 α ,7 β ,8 β (2S*,4S*),8 β]]-1,2,3,7,8,8 α -hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester

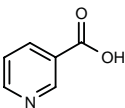


C24 H36 O5; Mol wt: 404.5434

Niacin

256792

3-Pyridinecarboxamide



C6 H5 N O2; Mol wt: 123.1105

ACTION – Combination of the HMG-CoA reductase inhibitor lovastatin and the hypolipidemic agent niacin.

INDICATION – Treatment of primary hypercholesterolemia and mixed dyslipidemia in patients previously treated with either component who require additional lipid modification for LDL or HDL cholesterol and triglycerides beyond that achieved by the individual components.

PRESENTATION – Tablets containing 500, 750 and 1000 mg of niacin in an extended-release formulation and 20 mg of lovastatin in an immediate-release formulation.

PROPRIETARY NAME – Advicor (US).

SOURCE – Kos Pharmaceuticals.

REFERENCES

1. El-Masri, B. *Future targets for lipid-lowering therapy.* 14th Int Symp Drugs Affect Lipid Metab (Sept 9-12, New York) 2001, 26.

2. Hunninghake, D.B. et al. *Dose-ranging and dose-sparing effects of a once-daily formulation of lovastatin and extended-release niacin in patients with hyperlipidemia.* 14th Int Symp Drugs Affect Lipid Metab (Sept 9-12, New York) 2001, 91.

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4. Insull, W. Jr. et al. *Dose-response effects of high-density lipoprotein cholesterol and multiple other lipoproteins of a new, once-daily formulation of lovastatin and extended-release niacin in patients with primary hypercholesterolemia.* 14th Int Symp Drugs Affect Lipid Metab (Sept 9-12, New York) 2001, 90.

5. Kashyap, M.L. et al. *New combination niacin/statin formulation shows pronounced effects on major lipoproteins and is well tolerated.* J Am Coll Cardiol 2000, 35(2, Suppl. A): 326A.

6. *First FDA-approved dual-component lipid modulator reaches market.* DailyDrugNews.com (Daily Essentials) 2002, Jan 30.

7. *Kos Pharmaceuticals receives approvable letter for niacin/lovastatin tablets.* DailyDrugNews.com (Daily Essentials) 2001, Aug 1.

8. *NDA submitted for combined niacin/lovastatin cholesterol product.* DailyDrugNews.com (Daily Essentials) 2000, Sept 28.

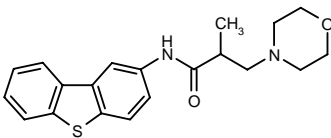
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10. *U.S. Federal Trade Commission clears alliance between Kos and DuPont.* DailyDrugNews.com (Daily Essentials) 2000, June 6.

TREATMENT OF OBESITY AND NUTRITIONAL DISORDERS

313062

N-(Dibenzo[b,d]thien-2-yl)-2-methyl-3-(4-morpholinyl)propionamide



C20 H22 N2 O2 S; Mol wt: 354.4718

ACTION – A representative compound from a series of dibenzo[*b,d*]thiophenes that acts as a neuropeptide Y (NPY) Y₅ receptor antagonist (IC₅₀ = 94 nM). Potentially useful for the treatment of obesity and nutritional disorders such as anorexia and bulimia, as well as related disorders including diabetes, dyslipidemia, hypertension and sleep disturbances.

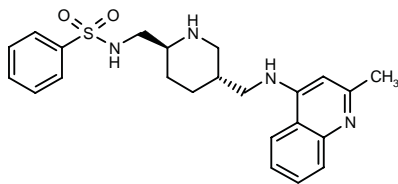
SOURCE – AstraZeneca.

REFERENCES

1. Block, M.H. et al. (AstraZeneca AB;AstraZeneca plc) *Amino subst. dibenzothiophene derivs. for the treatment of disorders mediated by the NP Y5 receptor*. WO 0185714.

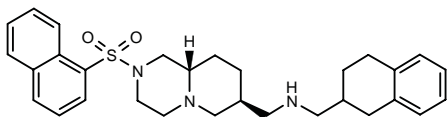
313063

trans-*N*-[5-(2-Methylquinolin-4-ylaminomethyl)piperidin-2-ylmethyl]benzenesulfonamide



C23 H28 N4 O2 S; Mol wt: 424.5662

ACTION – A neuropeptide Y (NPY) Y₅ receptor antagonist (IC₅₀ = 123 nM), potentially useful for the treatment of obesity and nutritional disorders such as anorexia and bulimia, as well as related disorders including diabetes, dyslipidemia, hypertension and sleep disturbances. Another exemplified compound is:



313064: C30 H37 N3 O2 S

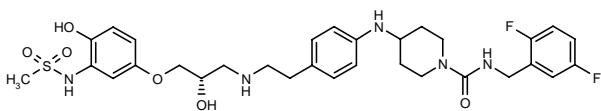
SOURCE – AstraZeneca.

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1. Block, M.H. and Schofield, P. (AstraZeneca AB;AstraZeneca plc) *Pyrido' 1,2-α pyrazine and piperidine derivs. as ligands for the neuropeptide Y Y5 receptor*. WO 0185730.

313155

N-(2,5-Difluorobenzyl)-4-[4-[2-[2(*S*)-hydroxy-3-[4-hydroxy-3-(methylsulfonamido)phenoxy]propylamino]-ethyl]phenylamino]piperidine-1-carboxamide



C31 H39 F2 N5 O6 S; Mol wt: 647.7401

ACTION – Potent β₃-adrenoceptor agonist (EC₅₀ = 1 nM for stimulation of cAMP accumulation in CHO cells expressing human receptors) with high selectivity over β₁- and β₂-adrenoceptors (EC₅₀ > 420 nM). Compound also showed selective β₃-adrenoceptor-agonist activity *in vivo* at 10 mg/kg i.p. in a β₃-adrenoceptor transgenic mouse model of thermogenesis. Potentially useful for the treatment of obesity and type 2 diabetes.

SOURCE – Wyeth Pharmaceuticals.

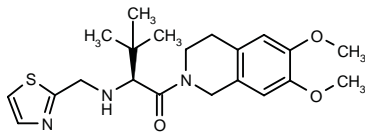
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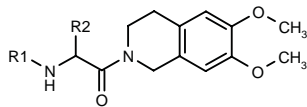
313157

1-(6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl)-3,3-dimethyl-2(*S*)-(thiazol-2-ylmethylamino)butan-1-one



C21 H29 N3 O3 S; Mol wt: 403.5441

ACTION – Orexin receptor antagonist that displayed an IC₅₀ of 0.049 μM against human orexin OX2 receptors and exhibited > 300-fold selectivity over OX1 receptors. Potentially useful for the treatment of obesity, eating disorders and sleep disorders. Other exemplified *N*-acyl-1,2,3,4-tetrahydroisoquinoline derivatives are:



Compound	R1	R2	Formula
313159	3,5-(Cl)2-PhCO	CH2Ph	C ₂₇ H ₂₆ Cl ₂ N ₂ O ₄
313165	4-Pyr-CH2	(S)-t-Bu	C ₂₃ H ₃₁ N ₃ O ₃
313166	3-Br-PhCH2	(S)-t-Bu	C ₂₄ H ₃₁ BrN ₂ O ₃

SOURCE – Banyu.

REFERENCES

1. Yamada, K. et al. (Banyu Pharmaceutical Co., Ltd.) *N-Acyltetrahydroisoquinoline derivs*. WO 0185693.

THERAPY OF INBORN ERRORS OF METABOLISM

AGALSIDASE ALFA

Prop INN; USAN

230384

α -Galactosidase (human clone λ AG18 isoenzyme A subunit protein moiety reduced) glycoform α

α -Galactosidase isoenzyme A, isolated from human cell line, clone RAG001, glycoform α

α -Galactosidase A

α -GAL

ACTION – α -Galactosidase A enzyme replacement therapy.

INDICATION – Long-term treatment of patients with a confirmed diagnosis of Fabry's disease (α -galactosidase A deficiency).

PRESENTATION – Solution for i.v. infusion containing 3.5 mg of agalsidase alfa.

PROPRIETARY NAME –Replagal (EU).

SOURCE – Transkaryotic Therapies.

REFERENCES

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- Phase I results reported for alpha-gal in Fabry's disease.* DailyDrugNews.com (Daily Essentials) 1998, March 4.
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17. *TKT achieves several milestones with three product platforms during 1999.* DailyDrugNews.com (Daily Essentials) 2000, Feb 22.

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19. *TKT files BLA for Fabry's disease treatment.* DailyDrugNews.com (Daily Essentials) 2000, June 20.

20. *TKT's Fabry's disease enzyme replacement therapy available for use in E.U.* DailyDrugNews.com (Daily Essentials) 2002, Jan 29.

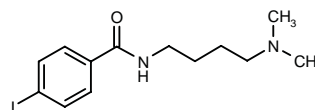
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22. *Transkaryotic Therapies initiates phase II program for Fabry's disease.* DailyDrugNews.com (Daily Essentials) 1998, Dec 17.

DIAGNOSTIC AGENTS

312328

N-[4-(Dimethylamino)butyl]-4-iodobenzamide



C13 H19 I N2 O; Mol wt: 346.2061

ACTION – Radiopharmaceutical agent, a benzamide derivative with high affinity for melanoma and more rapid clearance from nontarget tissues compared with the reference [¹²⁵I]-labeled N-(2-diethylaminoethyl)-4-iodobenzamide. Potentially useful for the scintigraphic detection of malignant melanoma and metastases.

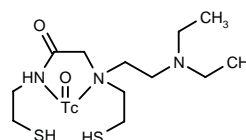
SOURCES – Université Blaise Pascal-Clermont-Ferrand II, Clermont-Ferrand (FR); INSERM, Paris Cedex (FR).

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- Moins, N. et al. *Synthesis, characterization and comparative biodistribution study of a new series of p-iodine-125 benzamides as potential melanoma imaging agents.* Nucl Med Biol 2001, 28(7): 799.

312560

[2-[N-[2-(N,N-Diethylamino)ethyl]-N-(2-sulfanylethyl)-amino]-N-(2-sulfanylethyl)acetamide]oxotechnetium



C12 H27 N3 O2 S2 Tc; Mol wt: 408.4023

ACTION – A technetium-labeled compound for use as an imaging agent in the diagnosis of cancer. Compound demonstrated tumor uptake both *in vitro* in human breast cancer MCF-7 cells and *in vivo* in mice bearing melanoma B16 nodules.

THERAPY OF INBORN ERRORS OF METABOLISM

AGALSIDASE ALFA

Prop INN; USAN

230384

α -Galactosidase (human clone λ AG18 isoenzyme A subunit protein moiety reduced) glycoform α

α -Galactosidase isoenzyme A, isolated from human cell line, clone RAG001, glycoform α

α -Galactosidase A

α -GAL

ACTION – α -Galactosidase A enzyme replacement therapy.

INDICATION – Long-term treatment of patients with a confirmed diagnosis of Fabry's disease (α -galactosidase A deficiency).

PRESENTATION – Solution for i.v. infusion containing 3.5 mg of agalsidase alfa.

PROPRIETARY NAME –Replagal (EU).

SOURCE – Transkaryotic Therapies.

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2. Schiffmann, R. et al. *Enzyme replacement therapy in Fabry disease. A randomized controlled trial.* JAMA - J Am Med Assoc 2001, 285(21): 2743.
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6. *EMA accepts MAA for Replagal as treatment of Fabry disease.* DailyDrugNews.com (Daily Essentials) 2000, July 20.
7. *Marketing approval obtained for Replagal in Israel, Switzerland and Czech Republic.* DailyDrugNews.com (Daily Essentials) 2002, Jan 9.
8. *Phase I results reported for alpha-gal in Fabry's disease.* DailyDrugNews.com (Daily Essentials) 1998, March 4.
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13. *Replagal receives European approval for Fabry's disease.* DailyDrugNews.com (Daily Essentials) 2001, Aug 9.
14. *Replagal receives positive opinion in E.U. for treatment of Fabry's disease.* DailyDrugNews.com (Daily Essentials) 2001, March 29.
15. *Replagal therapy for Fabry's disease approved in New Zealand and Iceland.* DailyDrugNews.com (Daily Essentials) 2001, Oct 25.

16. *Reversal of cardiomyopathy demonstrated in phase II trial of Replagal.* DailyDrugNews.com (Daily Essentials) 2001, May 21.

17. *TKT achieves several milestones with three product platforms during 1999.* DailyDrugNews.com (Daily Essentials) 2000, Feb 22.

18. *TKT and Sumitomo collaborate to commercialize Fabry's disease treatment in Asia.* DailyDrugNews.com (Daily Essentials) 1999, Jan 14.

19. *TKT files BLA for Fabry's disease treatment.* DailyDrugNews.com (Daily Essentials) 2000, June 20.

20. *TKT's Fabry's disease enzyme replacement therapy available for use in E.U.* DailyDrugNews.com (Daily Essentials) 2002, Jan 29.

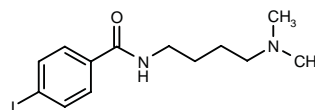
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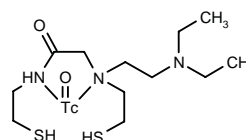
SOURCES – Université Blaise Pascal-Clermont-Ferrand II, Clermont-Ferrand (FR); INSERM, Paris Cedex (FR).

REFERENCES

1. Moins, N. et al. *Synthesis, characterization and comparative biodistribution study of a new series of p-iodine-125 benzamides as potential melanoma imaging agents.* Nucl Med Biol 2001, 28(7): 799.

312560

[2-[N-[2-(N,N-Diethylamino)ethyl]-N-(2-sulfanylethyl)-amino]-N-(2-sulfanylethyl)acetamide]oxotechnetium



C12 H27 N3 O2 S2 Tc; Mol wt: 408.4023

ACTION – A technetium-labeled compound for use as an imaging agent in the diagnosis of cancer. Compound demonstrated tumor uptake both *in vitro* in human breast cancer MCF-7 cells and *in vivo* in mice bearing melanoma B16 nodules.

SOURCES – Harvard College, Cambridge, MA (US);
Massachusetts Institute of Technology, Cambridge, MA
(US).

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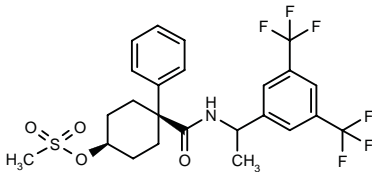
ANALGESIC AND ANESTHETIC
DRUGS

ANALGESIC DRUGS

313386

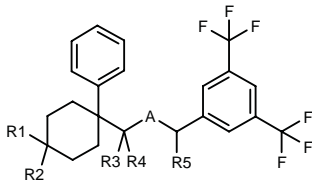
cis-Methanesulfonic acid 4-[*N*-[1-[3,5-bis(trifluoromethyl)phenyl]ethyl]carbamoyl]-4-phenylcyclohexyl ester

cis-*N*-[1-[3,5-bis(trifluoromethyl)phenyl]ethyl]-4-(methylsulfonyloxy)-1-phenylcyclohexanecarboxamide



C24 H25 F6 N O4 S; Mol wt: 537.5185

ACTION – Tachykinin NK₁ receptor antagonist with potential in the treatment of pain, inflammation, migraine, emesis, postherpetic neuralgia, depression and anxiety. Other exemplified cyclohexyl derivatives include the following:



Compound	R1	R2	R3	R4	R5	A	Isomer	Formula
313392	H	4-(4-F-Ph)-1-Pip	H	Me	H	O	trans	C ₃₄ H ₃₆ F ₇ NO
313398	H	NHCH2Ph	H	H	CH2OH	O	cis	C ₃₀ H ₃₁ F ₆ NO ₂
313402	H	1-pyrrolidinyl-CH2CH2	H	H	CH2OH	O	cis	C ₂₉ H ₃₅ F ₆ NO ₂
313406	H	4-(4-F-Ph)-1-Pip	-O-	Me	NH	trans		C ₃₄ H ₃₅ F ₇ N ₂ O
313409	H	N(Me)CH2Ph	-O-	Me	NH	trans		C ₃₁ H ₃₂ F ₆ N ₂ O
313411	H	4-morpholinyl-CH2	-O-	Me	NH	trans		C ₂₈ H ₃₂ F ₆ N ₂ O ₂
313414		-OCH2CH2O-	H	H	H	O		C ₂₄ H ₂₄ F ₆ O ₃
313417	H	CH2OH	-O-	Me	NH	trans		C ₂₄ H ₂₅ F ₆ NO ₂

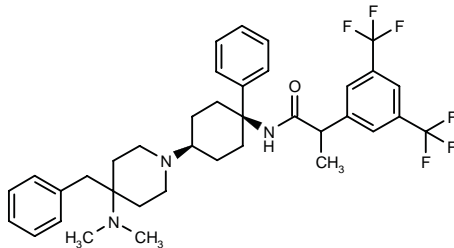
SOURCE – Merck Sharp & Dohme.

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1. Castro Pineiro, J.L. et al. (Merck Sharp & Dohme Ltd.) *Cyclohexyl derivs. and their use as therapeutic agents*. WO 0187866.

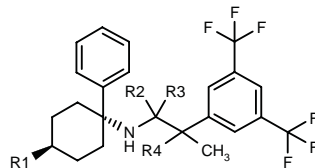
313429

cis-*N*-[4-[4-Benzyl-4-(dimethylamino)piperidin-1-yl]-1-phenylcyclohexyl]-2-[3,5-bis(trifluoromethyl)phenyl]propionamide



C37 H43 F6 N3 O; Mol wt: 659.7547

ACTION – Tachykinin NK₁ receptor antagonist with potential in the treatment of pain, inflammation, migraine, emesis, postherpetic neuralgia, depression and anxiety. Other exemplified cyclohexane derivatives include the following:



Compound	R1	R2	R3	R4	Formula
313431	4-OH-4-(PhCH2)-1-Pip	-O-	H		C ₃₅ H ₃₈ F ₆ N ₂ O ₂
313433	t-BuOCONHCH2CH2NH	-O-	H		C ₃₀ H ₃₇ F ₆ N ₃ O ₃
313436	4-(4-F-Ph)-1-Pip	-O-	Me		C ₃₅ H ₃₇ F ₇ N ₂ O
313437	NHCH2Ph	-O-	H		C ₃₀ H ₃₀ F ₆ N ₂ O
313438	N(CH2Ph)CH2CO2Me	-O-	H		C ₃₃ H ₃₄ F ₆ N ₂ O ₃
313440	CH2NH2	-O-	H		C ₂₄ H ₂₆ F ₆ N ₂ O
313442	4-(4-F-Ph)-1-Pip	H	H	H	C ₃₄ H ₃₇ F ₇ N ₂

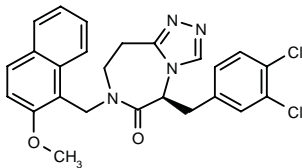
SOURCE – Merck Sharp & Dohme.

REFERENCES

1. Castro Pineiro, J.L. et al. (Merck Sharp & Dohme Ltd.) *Cyclohexane derivs. and their use as therapeutic agents*. WO 0187838.

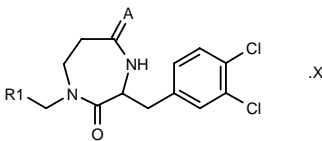
313756

5(S)-(3,4-Dichlorobenzyl)-7-(2-methoxynaphthalen-1-ylmethyl)-6,7,8,9-tetrahydro-5H-[1,2,4]triazolo[4,3-d]-[1,4]diazepin-6-one

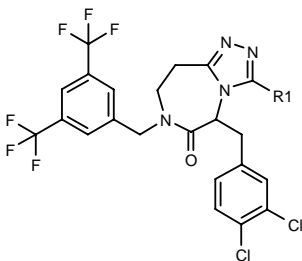


C25 H22 Cl2 N4 O2; Mol wt: 481.3808

ACTION – Tachykinin NK₁ receptor antagonist with a pK_i of 8.76 at human NK₁ receptors expressed in CHO cells. Potentially useful for the treatment of pain, migraine, arthritis, asthma, inflammatory bowel disease, Parkinson’s disease, Alzheimer’s disease, multiple sclerosis, allergic rhinitis, ulcerative colitis, Crohn’s disease, urinary incontinence, anxiety, depression, psychosis, motion sickness, etc. Other exemplified 1,4-diazepan-2,5-dione derivatives are:



Compound	R1	A	X	Isomer	Formula
313757	3,5-(CF3)2-Ph	N(Pr)	HCl		C ₂₄ H ₂₃ Cl ₂ F ₆ N ₃ O.HCl
313759	2-EtO-1-Naph	O			C ₂₆ H ₂₄ Cl ₂ N ₂ O ₃
313762	2-Me-1-Naph	O		S	C ₂₄ H ₂₂ Cl ₂ N ₂ O ₂
313763	2-MeO-1-Naph	O		S	C ₂₄ H ₂₂ Cl ₂ N ₂ O ₃



Compound	R1	Formula
313758	1-Me-2-Pip	C ₂₈ H ₂₇ Cl ₂ F ₆ N ₅ O
313760	CH2N(Me)2	C ₂₅ H ₂₃ Cl ₂ F ₆ N ₅ O
313761	4-morpholinyl-CH2CH2	C ₂₈ H ₂₇ Cl ₂ F ₆ N ₅ O ₂
313764	H	C ₂₂ H ₁₆ Cl ₂ F ₆ N ₄ O

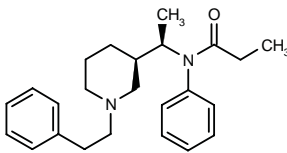
SOURCE – Roche.

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1. Galley, G. et al. (F. Hoffmann-La Roche AG) 1,4-Diazepan-2,5-dione derivs. and their use as NK-1 receptor antagonists. WO 0190083.

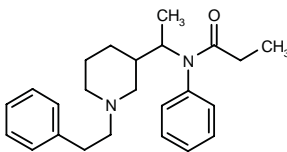
314078

N-Phenyl-N-[1(R)-[1-(2-phenylethyl)piperidin-3(R)-yl]-ethyl]propionamide



C24 H32 N2 O; Mol wt: 364.5298

ACTION – Analgesic agent that acts as a ligand for opioid and other G-protein-coupled receptors, as well as ion channels. It demonstrated *in vivo* analgesic activity in the rat tail-flick latency test following oral administration (0.20 mg/kg). Other specifically claimed heterocyclic compounds are:



Compound	Isomer	Formula
314079	1R,3’S	C ₂₄ H ₃₂ N ₂ O
314080	1S,3’S	C ₂₄ H ₃₂ N ₂ O
314081	1S,3’R	C ₂₄ H ₃₂ N ₂ O

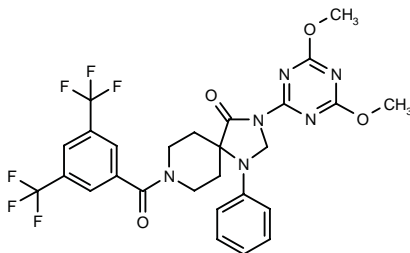
SOURCE – Sepracor.

REFERENCES

1. Cuny, G.D. et al. (Sepracor Inc.) Heterocyclic analgesic cpds. and method of use thereof. WO 0192226.

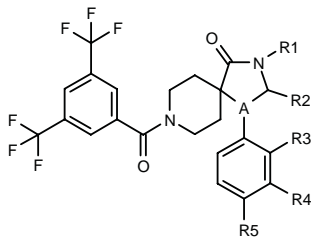
314364

8-[3,5-Bis(trifluoromethyl)benzoyl]-3-(4,6-dimethoxy-1,3,5-triazin-2-yl)-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one

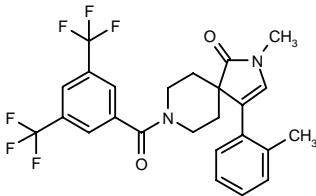


C27 H24 F6 N6 O4; Mol wt: 610.5126

ACTION – Tachykinin NK₁ receptor antagonist (pK_i = 8.66), potentially useful for the treatment of pain, migraine, Alzheimer’s disease, multiple sclerosis, morphine withdrawal, edema, arthritis, asthma, allergic rhinitis, ulcerative colitis, Crohn’s disease, ocular injury and ocular inflammatory diseases, urinary incontinence, anxiety, depression, psychosis and motion sickness. Other exemplified nitrogen-containing spiro compounds are:



Compound	R1	R2	R3	R4	R5	A	Formula
314365	3,5-(Cl)2-2-Pyr	H	H	H	H	N	C ₂₇ H ₂₀ Cl ₂ F ₆ N ₄ O ₂
314366	4,6-(MeO)2-1,3,5-triazin-2-yl	H	H	Cl	Cl	N	C ₂₇ H ₂₂ Cl ₂ F ₆ N ₆ O ₄
314367	3-Pyr-CH ₂	H	Me	H	H	N	C ₂₉ H ₂₆ F ₆ N ₄ O ₂
314368	1-pyrrolidinyl-CH ₂ CH ₂	H	Me	H	H	N	C ₂₉ H ₃₂ F ₆ N ₄ O ₂
314369	Me	H	Cl	H	H	N	C ₂₃ H ₂₀ ClF ₆ N ₃ O ₂
314370	H	Me	H	H	H	N	C ₂₃ H ₂₁ F ₆ N ₃ O ₂
314372	CH ₂ CH ₂ OMe	Me	Me	H	H	N	C ₂₇ H ₂₉ F ₆ N ₃ O ₃
314374	H	H	Me	H	H	CH	C ₂₄ H ₂₂ F ₆ N ₂ O ₂



314373: C₂₅ H₂₂ F₆ N₂ O₂

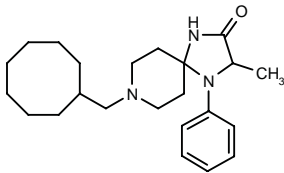
SOURCE – Roche.

REFERENCES

1. Galley, G. et al. (F. Hoffmann-La Roche AG) 1,3,8-Triaza-spiro[4,5]decan-4-one derivs. as neurokinin receptor antagonists. WO 0194346.

314828

8-(Cyclooctylmethyl)-3-methyl-4-phenyl-1,4,8-triazaspiro-[4.5]decan-2-one



C₂₃ H₃₅ N₃ O; Mol wt: 369.5495

ACTION – A representative compound from a series of 1,4,8-triazaspiro[4.5]decan-2-one derivatives with nociceptin (N/OFQ)-antagonist activity. This compound inhibited the binding of [¹²⁵I]-nociceptin to N/OFQ receptors expressed in CHO cells with an IC₅₀ of 11 nM. It was also shown to inhibit nociceptin-induced G-protein activation with an IC₅₀ value of 400 nM. Potentially useful for the treatment of pain, narcotic analgesic tolerance, obesity, Alzheimer’s disease, dementia, schizophrenia, Parkinson’s disease, depression, diabetes, polyuria and hypotension.

SOURCE – Banyu.

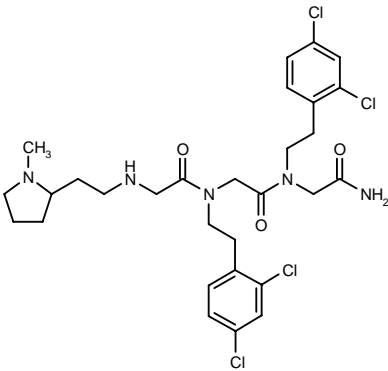
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1. Satoh, A. et al. (Banyu Pharmaceutical Co., Ltd.) 4-Oxoimidazolidine-2-spiro-nitrogenous heterocycle cpds. WO 0196337.

DD-161515

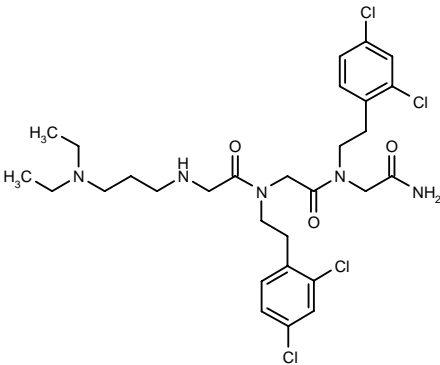
316263

N-[2-(1-Methylpyrrolidin-2-yl)ethyl]-glycyl-N-[2-(2,4-dichlorophenyl)ethyl]-glycyl-N²-[2-(2,4-dichlorophenyl)ethyl]glycinamide



C₂₉ H₃₇ Cl₄ N₅ O₃; Mol wt: 645.4553

ACTION – Potent, selective and noncompetitive vanilloid VR1 receptor antagonist (IC₅₀ = 0.7 μM) that prevents capsaicin-induced Ca²⁺ influx in cultured trigeminal neurons in a reversible manner. In murine models of nociception and hyperalgesia, compound significantly suppressed thermal nociception in the hot-plate test following i.p. administration and was effective against capsaicin-induced pain and neurogenic inflammation and nitrogen mustard-induced thermal hyperalgesia, without altering responses to mechanical stimuli. Potentially useful as an analgesic agent for the treatment of inflammatory pain. Another related compound is:



DD-191515 [316264]: C₂₉ H₃₉ Cl₄ N₅ O₃

SOURCES – CSIC, Madrid (ES); DiverDrugs; Universidad Miguel Hernández, Elche (ES); Universidad de Valencia, Valencia (ES).

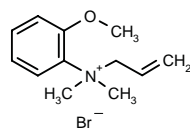
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ADJUNCTS TO ANESTHESIA

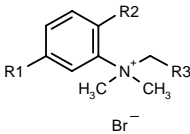
314236

N-Allyl-2-methoxy-N,N-dimethylbenzenaminium bromide



C12 H18 Br N O; Mol wt: 272.1842

ACTION – Acetylcholinesterase inhibitor (IC₅₀ = 1-3 μM) proven to reverse vecuronium-induced block of guinea pig hemidiaphragm with an EC₅₀ value of 2.89 μM. In anesthetized cats, compound reversed vecuronium-induced neuromuscular block with an ED₅₀ value of 0.22 μmol/kg i.v., causing fewer cardiovascular side effects than combination therapy with neostigmine plus glycopyrrolate or edrophonium plus atropine. Potentially useful for the reversal of neuromuscular block in anesthetic practice. Other related compounds are:



Compound	R1	R2	R3	Formula
314235	H	OH	vinyl	C ₁₁ H ₁₆ BrNO
314237	3,4-(MeO)2-Ph	COCH2O	H	C ₂₅ H ₂₈ BrNO ₄

SOURCE – Organon.

REFERENCES

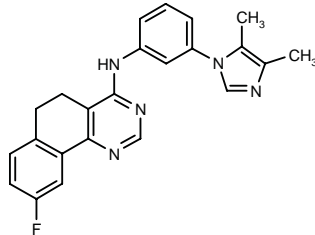
1. Grove, S.J.A. et al. *Oxanyliniums as acetylcholinesterase inhibitors for the reversal of neuromuscular block*. *Bioorg Med Chem Lett* 2002, 12(2): 193.

PSYCHOPHARMACOLOGIC DRUGS

ANXIOLYTICS

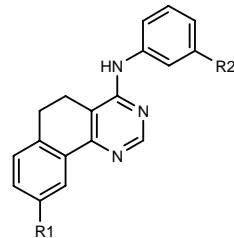
313311

N-[3-(4,5-Dimethyl-1H-imidazol-1-yl)phenyl]-9-fluoro-5,6-dihydrobenzo[h]quinazolin-4-amine



C23 H20 F N5; Mol wt: 385.4440

ACTION – Agent that acts at 5-HT_{2C} receptors, particularly as a 5-HT_{2C} antagonist, claimed for use in the treatment of anxiety, depression, obsessive–compulsive disorders, migraine, anorexia, Alzheimer’s disease, sleep disorders, bulimia, panic attacks, drug abuse, schizophrenia and disorders related to spinal cord trauma or head injury. Other heterocyclic compounds are:



Compound	R1	R2	Formula
313312	F	4-Me-1-imidazolyl	C ₂₂ H ₁₈ FN ₅
313313	F	1,2-(Me)2-5-imidazolyl	C ₂₃ H ₂₀ FN ₅
313314	H	1,2-(Me)2-5-imidazolyl	C ₂₃ H ₂₁ N ₅
313315	H	4,5-(Me)2-1-imidazolyl	C ₂₃ H ₂₁ N ₅
313316	H	4-Me-1-imidazolyl	C ₂₂ H ₁₉ N ₅

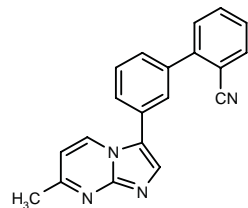
SOURCE – Fujisawa.

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313788

3’-(7-Methylimidazo[1,2-a]pyrimidin-3-yl)biphenyl-2-carbonitrile



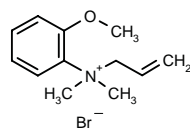
C20 H14 N4; Mol wt: 310.3586

ACTION – Selective ligand for α2, α3 and/or α5 GABA_A receptors, potentially useful for the treatment of anxiety, convulsions and cognitive disorders including Alzheimer’s disease. Other exemplified 3-phenylimidazo[1,2-a]pyrimidine derivatives are:

ADJUNCTS TO ANESTHESIA

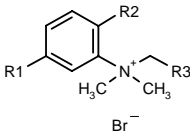
314236

N-Allyl-2-methoxy-N,N-dimethylbenzenaminium bromide



C12 H18 Br N O; Mol wt: 272.1842

ACTION – Acetylcholinesterase inhibitor (IC₅₀ = 1-3 μM) proven to reverse vecuronium-induced block of guinea pig hemidiaphragm with an EC₅₀ value of 2.89 μM. In anesthetized cats, compound reversed vecuronium-induced neuromuscular block with an ED₅₀ value of 0.22 μmol/kg i.v., causing fewer cardiovascular side effects than combination therapy with neostigmine plus glycopyrrolate or edrophonium plus atropine. Potentially useful for the reversal of neuromuscular block in anesthetic practice. Other related compounds are:



Compound	R1	R2	R3	Formula
314235	H	OH	vinyl	C ₁₁ H ₁₆ BrNO
314237	3,4-(MeO)2-Ph	COCH2O	H	C ₂₅ H ₂₈ BrNO ₄

SOURCE – Organon.

REFERENCES

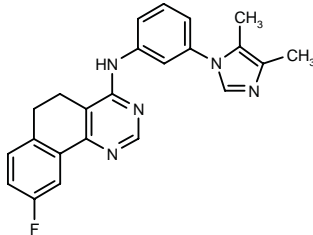
1. Grove, S.J.A. et al. *Oxanyliniums as acetylcholinesterase inhibitors for the reversal of neuromuscular block*. *Bioorg Med Chem Lett* 2002, 12(2): 193.

PSYCHOPHARMACOLOGIC DRUGS

ANXIOLYTICS

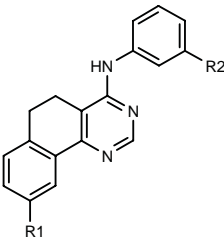
313311

N-[3-(4,5-Dimethyl-1H-imidazol-1-yl)phenyl]-9-fluoro-5,6-dihydrobenzo[h]quinazolin-4-amine



C23 H20 F N5; Mol wt: 385.4440

ACTION – Agent that acts at 5-HT_{2C} receptors, particularly as a 5-HT_{2C} antagonist, claimed for use in the treatment of anxiety, depression, obsessive–compulsive disorders, migraine, anorexia, Alzheimer’s disease, sleep disorders, bulimia, panic attacks, drug abuse, schizophrenia and disorders related to spinal cord trauma or head injury. Other heterocyclic compounds are:



Compound	R1	R2	Formula
313312	F	4-Me-1-imidazolyl	C ₂₂ H ₁₈ FN ₅
313313	F	1,2-(Me)2-5-imidazolyl	C ₂₃ H ₂₀ FN ₅
313314	H	1,2-(Me)2-5-imidazolyl	C ₂₃ H ₂₁ N ₅
313315	H	4,5-(Me)2-1-imidazolyl	C ₂₃ H ₂₁ N ₅
313316	H	4-Me-1-imidazolyl	C ₂₂ H ₁₉ N ₅

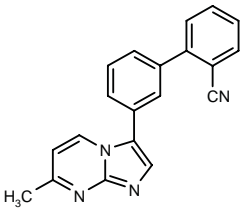
SOURCE – Fujisawa.

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1. Yamada, A. et al. (Fujisawa Pharmaceutical Co., Ltd.) *N-Containing heterocyclic cpds*. WO 0187845.

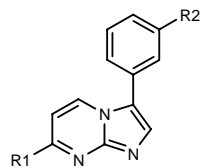
313788

3’-(7-Methylimidazo[1,2-a]pyrimidin-3-yl)biphenyl-2-carbonitrile



C20 H14 N4; Mol wt: 310.3586

ACTION – Selective ligand for α2, α3 and/or α5 GABA_A receptors, potentially useful for the treatment of anxiety, convulsions and cognitive disorders including Alzheimer’s disease. Other exemplified 3-phenylimidazo[1,2-a]pyrimidine derivatives are:



Compound	R1	R2	Formula
313789	H	2-CN-Ph	C ₁₉ H ₁₂ N ₄
313790	t-Bu	2-CN-Ph	C ₂₃ H ₂₀ N ₄
313791	CH=NOH	2-CN-Ph	C ₂₀ H ₁₃ N ₅ O
313793	CHF2	2-CN-Ph	C ₂₀ H ₁₂ F ₂ N ₄
313794	Me	2-Pyr	C ₁₈ H ₁₄ N ₄
313795	CF3	2-(1,2,4-triazol-1-yl)-Ph	C ₂₁ H ₁₃ F ₃ N ₆
313796	CF3	2-CN-4-F-Ph	C ₂₀ H ₁₀ F ₄ N ₄
313797	CF3	3-Pyr	C ₁₈ H ₁₁ F ₃ N ₄

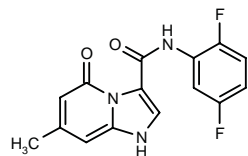
SOURCE – Merck Sharp & Dohme.

REFERENCES

1. Blackaby, W.P. et al. (Merck Sharp & Dohme Ltd.) 3-Phenyl-imidazo-pyrimidine derivs. as ligands for GABA receptors. WO 0190108.

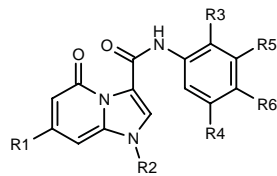
313955

N-(2,5-Difluorophenyl)-7-methyl-5-oxo-1,5-dihydro-imidazo[1,2-a]pyridine-3-carboxamide



C15 H11 F2 N3 O2; Mol wt: 303.2669

ACTION – Agent with affinity for the benzodiazepine site of GABA_A receptors, potentially useful for the treatment of anxiety, depression, sleep disorders and Alzheimer’s disease. Other specifically claimed imidazo[1,2-a]pyridine derivatives include the following:



Compound	R1	R2	R3	R4	R5	R6	Formula
313956	H	H	F	H	H	H	C ₁₄ H ₁₀ FN ₃ O ₂
313957	H	H	F	H	CF3	H	C ₁₅ H ₉ F ₄ N ₃ O ₂
313958	H	H	H	H	H	OCF3	C ₁₅ H ₁₀ F ₃ N ₃ O ₃
313959	H	H	F	H	H	OEt	C ₁₆ H ₁₄ FN ₃ O ₃
313960	H	H	H	H	-CH=CHCH=CH-		C ₁₈ H ₁₃ N ₃ O ₂
313961	Me	H	H	H	H	H	C ₁₅ H ₁₃ N ₃ O ₂
313962	Me	H	H	H	H	OH	C ₁₅ H ₁₃ N ₃ O ₃
313963	Me	Et	H	H	H	OH	C ₁₇ H ₁₇ N ₃ O ₃

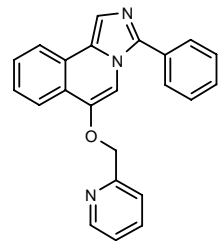
SOURCE – Neurogen.

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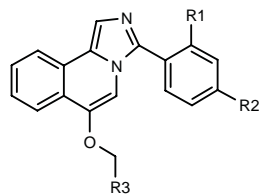
313964

3-Phenyl-6-(pyridin-2-ylmethoxy)imidazo[5,1-a]isoquinoline



C23 H17 N3 O; Mol wt: 351.4073

ACTION – Agent with affinity for the benzodiazepine site of GABA_A receptors, potentially useful for the treatment of anxiety, depression, sleep disorders and Alzheimer’s disease. Other specifically claimed imidazo[5,1-a]isoquinoline derivatives include the following:



Compound	R1	R2	R3	Formula
313965	F	H	2-Pyr	C ₂₃ H ₁₆ FN ₃ O
313966	H	Cl	2-Pyr	C ₂₃ H ₁₆ ClN ₃ O
313967	H	CF3	2-Pyr	C ₂₄ H ₁₆ F ₃ N ₃ O
313968	H	Et	2-Pyr	C ₂₅ H ₂₁ N ₃ O
313969	H	Me	2-imidazolyl	C ₂₂ H ₁₈ N ₄ O
313970	H	H	Ph	C ₂₄ H ₁₈ N ₂ O
313971	H	H	1-Me-1,2,3-triazol-4-yl	C ₂₁ H ₁₇ N ₅ O
313972	H	F	1-Me-1,2,3-triazol-4-yl	C ₂₁ H ₁₆ FN ₅ O

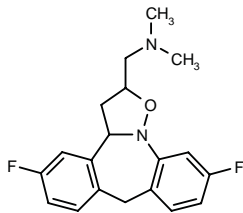
SOURCE – Neurogen.

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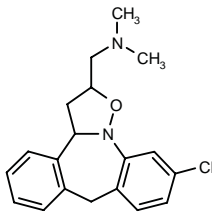
314256

N-(5,11-Difluoro-2,3,3a,8-tetrahydrodibenzo[*c,f*]isoxazolo[2,3-*a*]azepin-2-ylmethyl)-N,N-dimethylamine



C19 H20 F2 N2 O; Mol wt: 330.3760

ACTION – Potential anxiolytic agent and antidepressant with high affinity for both 5-HT_{2A} and 5-HT_{2C} receptors (pIC₅₀ = 7.97 and 8.21, respectively) and histamine H₁ receptors (pIC₅₀ = 7.77), and high selectivity over a panel of receptors including adrenergic, dopaminergic and histaminergic receptors (pIC₅₀ = 6 or less). Compound exhibited strong 5-HT-antagonist activity in a model of *m*-chlorophenylpiperazine-induced anxiety in rats, with ED₅₀ values of 0.04 and 0.63 mg/kg after s.c. and p.o. administration, respectively. Another related compound is:



314255: C19 H21 Cl N2 O

SOURCE – Janssen.

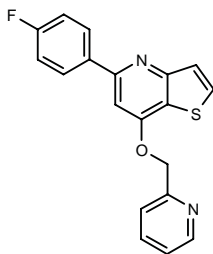
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1. Sipido, V.K. et al. (Janssen Pharmaceutica NV) *Substd. tetracyclic azepine derivs. which have affinity for 5-HT₂ receptors*. EP 0789701, JP 1998508308, US 5552399, WO 9614320.

2. Andrés, J.I. et al. *Synthesis and structure-activity relationship of 2-(aminoalkyl)-2,3,3a,8-tetrahydrodibenzo[*c,f*]isoxazolo[2,3-*a*]azepine derivatives: A novel series of 5-HT_{2A/2C} receptor antagonists. Part 2*. Bioorg Med Chem Lett 2002, 12(2): 249.

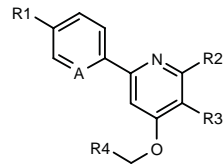
314909

5-(4-Fluorophenyl)-7-(pyridin-2-ylmethoxy)thieno[3,2-*b*]pyridine



C19 H13 F N2 O S; Mol wt: 336.3887

ACTION – Agent with affinity for the benzodiazepine site of the GABA_A receptor, potentially useful for the treatment of anxiety, depression, sleep disorders and Alzheimer's disease. Other specifically claimed aryl fused 4-alkoxy pyridines are:



Compound	R1	R2,R3	R4	A	Formula
314912	H	-CH=CHCH=CH-	2(R)-(CH2OH)-1-pyrrolidinyl-CO	CH	C ₂₂ H ₂₂ N ₂ O ₃
314913	H	-CH=CHS-	CON(Et) ₂	CH	C ₁₉ H ₂₀ N ₂ O ₂ S
314915	F	-CH=CHCH=CH-	2-(CH2OH)-1-pyrrolidinyl-CO	N	C ₂₁ H ₂₀ FN ₃ O ₃
314916	H	-CH=CHCH=CH-	1-Me-1,2,3-triazol-4-yl	CH	C ₁₉ H ₁₆ N ₄ O
314917	F	-CH=CHN=CH-	2-(CH2OH)-1-pyrrolidinyl-CO	CH	C ₂₁ H ₂₀ FN ₃ O ₃

SOURCE – Neurogen.

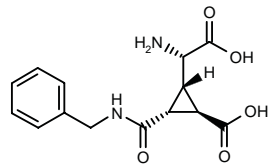
REFERENCES

1. Cai, G. et al. (Neurogen Corp.) *Aryl fused subst. 4-oxy-pyridines*. WO 0200623.

ANTIPSYCHOTIC DRUGS

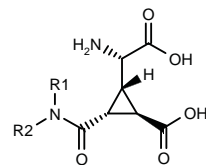
314018

(1*R**,2*S**,3*R**)-2-[1(*S**)-Amino-1-carboxymethyl]-3-(*N*-benzylcarbamoyl)cyclopropanecarboxylic acid



C14 H16 N2 O5; Mol wt: 292.2894

ACTION – Excitatory amino acid modulator that acts as an agonist at metabotropic glutamate receptors. Potentially useful for the treatment of neurodegenerative diseases and as an antipsychotic, anxiolytic, anticonvulsant, analgesic and antiemetic agent. Other exemplified compounds are:



Compound	R1	R2	Formula
314019	NHCOPh	H	C ₁₄ H ₁₅ N ₃ O ₆
314020	Me	Me	C ₉ H ₁₄ N ₂ O ₅
314021	NHPh	H	C ₁₃ H ₁₆ ClN ₃ O ₅
314022	CH2CH2Ph	H	C ₁₅ H ₁₈ N ₂ O ₅
314023	CH2CH2N(Me) ₂	H	C ₁₁ H ₁₉ N ₃ O ₅

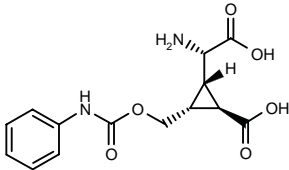
SOURCE – Lilly.

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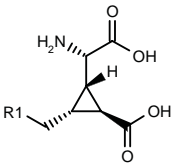
314024

(1*R**,2*S**,3*R**)-2-[1(*S**)-Amino-1-carboxymethyl]-3-(*N*-phenylcarbamoyloxymethyl)cyclopropanecarboxylic acid



C14 H16 N2 O6; Mol wt: 308.2884

ACTION – Excitatory amino acid modulator that acts as an agonist at metabotropic glutamate receptors. Potentially useful for the treatment of neurodegenerative diseases and as an antipsychotic, anxiolytic, anticonvulsant, analgesic and antiemetic agent. Other exemplified compounds are:



Compound	R1	Formula
314025	4-MeO-PhNHCOO	C ₁₅ H ₁₈ N ₂ O ₇
314026	3-NO2-PhNHCOO	C ₁₄ H ₁₅ N ₃ O ₈
314027	OC(=O)NCH2Ph	C ₁₅ H ₁₈ N ₂ O ₆
314028	1-Naph-NHCOO	C ₁₈ H ₁₈ N ₂ O ₆
314029	NHCONHCH2Ph	C ₁₅ H ₁₉ N ₃ O ₅
314030	NHCSNHPh	C ₁₄ H ₁₇ N ₃ O ₄ S

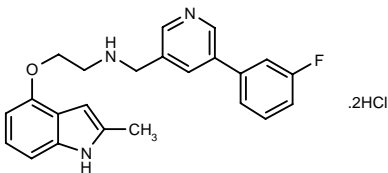
SOURCE – Lilly.

REFERENCES

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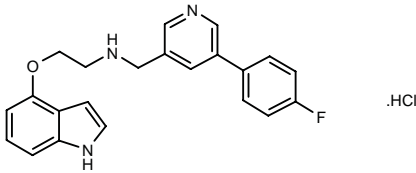
314819

N-[5-(3-Fluorophenyl)pyridin-3-ylmethyl]-2-(2-methyl-1*H*-indol-4-yloxy)ethylamine dihydrochloride



C23 H22 F N3 O . 2HCl; Mol wt: 448.3666

ACTION – Agent with affinity for dopamine D2 and 5-HT_{1A} receptors, potentially useful for the treatment of CNS disorders, particularly schizophrenia. Another exemplified compound within this series of pyridine derivatives is:



314821: C22 H20 F N3 O . HCl

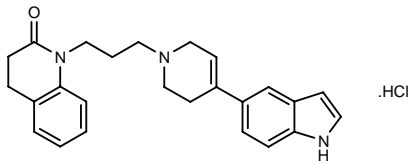
SOURCE – Merck KGaA.

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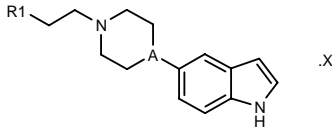
314892

1-[3-[4-(1*H*-Indol-5-yl)-1,2,3,6-tetrahydropyridin-1-yl]prop-yl]-1,2,3,4-tetrahydroquinolin-2-one hydrochloride

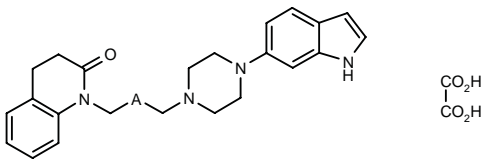


C25 H27 N3 O . HCl; Mol wt: 421.9692

ACTION – Dual dopamine D4 and 5-HT_{2A} receptor ligand, as demonstrated by its ability to inhibit the binding of [³H]-YM-09151-2 to D4 receptors expressed in CHO cells with an IC₅₀ of 0.97 nM, and the binding of [³H]-ketanserin to 5-HT_{2A} receptors in rat brain preparations with an IC₅₀ of 6.6 nM. Potentially useful for the treatment of schizophrenia, anxiety, panic, obsessive–compulsive disorders, side effects associated with conventional antipsychotic agents, migraine, attention deficit hyperactivity disorder and sleep disorders. Other exemplified indole derivatives are:



Compound	R1	A	X	Formula
314894	2-oxo-1,2,3,4-tetrahydro-1-quinolinyl-CH2	N	HCl	C ₂₄ H ₂₈ N ₄ O.HCl
314895	2-oxo-1,2,3,4-tetrahydro-1-quinolinyl-CH2CH2	N	HCl	C ₂₅ H ₃₀ N ₄ O.HCl
314900	2-oxo-1,2,3,4-tetrahydro-1-quinolyl	N	oxalate	C ₂₃ H ₂₆ N ₄ O .C ₂ H ₂ O ₄
314901	2-oxo-1,2,3,4-tetrahydro-1-quinolinyl-CH2	CH	HCl	C ₂₅ H ₂₈ N ₃ O.HCl
314902	3-oxo-3,4-dihydro-2H-1,4-benzoxazin-4-yl-CH2CH2	N	HCl	C ₂₄ H ₂₈ N ₄ O ₂ .HCl
314906	1-oxo-1,2,3,4-tetrahydro-2-isoquinolinyl-CH2CH2	N	HCl	C ₂₅ H ₃₀ N ₄ O.HCl
314907	1,2,3,4-tetrahydro-1-quinolyl-CH2	N	HCl	C ₂₄ H ₃₀ N ₄ .HCl
314908	1,2,3,4-tetrahydro-1-quinolinyl-CH2CH2	N	HCl	C ₂₅ H ₃₂ N ₄ .HCl
314910	1,2,3,4-tetrahydro-2-isoquinolyl-CO	N	HCl	C ₂₄ H ₂₈ N ₄ O.HCl
314911	1,2,3,4-tetrahydro-2-isoquinolinyl-COCH2	N	HCl	C ₂₅ H ₃₀ N ₄ O.HCl



Compound	A	Formula
314896	-CH2-	C ₂₄ H ₂₈ N ₄ O.C ₂ H ₂ O ₄
314898	-(CH2)2-	C ₂₅ H ₃₀ N ₄ O.C ₂ H ₂ O ₄

SOURCE – Lundbeck.

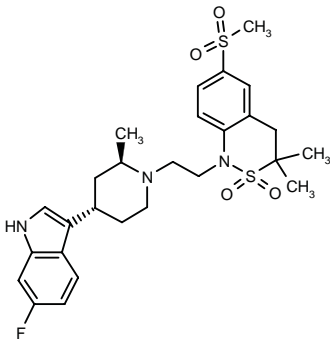
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TREATMENT OF MOOD DISORDERS

313282

1-[2-[4(S)-(6-Fluoro-1*H*-indol-3-yl)-2(*R*)-methylpiperidin-1-yl]ethyl]-3,3-dimethyl-6-(methylsulfonyl)-3,4-dihydro-1*H*-2,1-benzothiazine 2,2-dioxide



C27 H34 F N3 O4 S2; Mol wt: 547.7126

ACTION – A representative compound from a series of piperidine-substituted indoles with the ability to increase the release of 5-HT through an interaction with 5-HT receptors, particularly 5-HT_{1B}, 5-HT_{1D} and 5-HT_{2A} receptor subtypes. Potentially useful for the treatment of a wide range of disorders, particularly depression and obsessive–compulsive disorder. Other applications include obesity, bulimia, drug abuse, pain, hypertension, memory loss, sexual dysfunction, anxiety, schizophrenia, gastrointestinal disorders, cardiovascular disorders, smoking cessation, emesis, epilepsy, Alzheimer’s disease and sleep disorders.

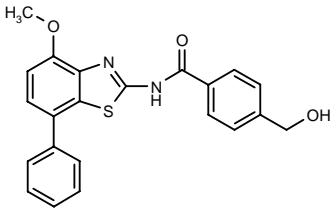
SOURCE – Lilly.

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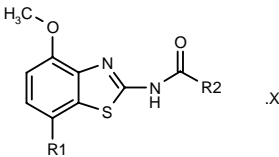
314788

4-(Hydroxymethyl)-*N*-(4-methoxy-7-phenylbenzothiazol-2-yl)benzamide



C22 H18 N2 O3 S; Mol wt: 390.4612

ACTION – Adenosine A_{2A} receptor antagonist (pK_i = 9.3), particularly useful for the treatment of depression, neurodegenerative disorders and Parkinson’s disease. Further applications include Alzheimer’s disease, schizophrenia, anxiety, pain, respiratory deficits, asthma, allergy, hypoxia, ischemia, seizures, drug abuse and epilepsy, and also as a sedative, muscle relaxant and cardioprotectant. Other exemplified benzothiazole derivatives include the following:



Compound	R1	R2	X	Formula
314794	Ph	5-Me-2-furyl		C ₂₀ H ₁₆ N ₂ O ₃ S
314797	Ph	3-Pyr		C ₂₀ H ₁₅ N ₃ O ₂ S
314799	3-Pyr	5-Me-2-thienyl		C ₁₉ H ₁₅ N ₃ O ₂ S ₂
314805	3-NH2-Ph	5-Me-2-thienyl		C ₂₀ H ₁₇ N ₃ O ₂ S ₂
314811	Ph	4-(1-imidazolyl-CH2)-Ph	HCl	C ₂₅ H ₂₀ N ₄ O ₂ S.HCl
314816	Ph	4-(NH2CH2)-Ph	HCl	C ₂₂ H ₁₉ N ₃ O ₂ S.HCl
314823	Ph	4-[3(S)-N(Me)2-1-pyrrolidinyl-CH2]-Ph	2HCl	C ₂₈ H ₃₀ N ₄ O ₂ S.2HCl
314825	4-morpholinyl	4-Cl-3-(1-pyrrolidinyl-CH2)-Ph		C ₂₄ H ₂₇ ClN ₄ O ₃ S
314827	4-morpholinyl	4-(2-Me-1-imidazolyl-CH2)-Ph		C ₂₄ H ₂₅ N ₃ O ₃ S
314831	4-morpholinyl	4-[CO2MeN(Me)CH2]-Ph		C ₂₃ H ₂₆ N ₄ O ₅ S

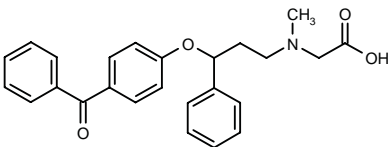
SOURCE – Roche.

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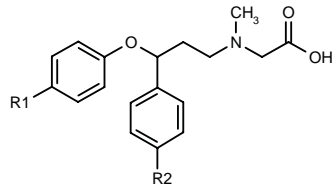
314934

2-[*N*-[3-(4-Benzoylphenoxy)-3-phenylpropyl]-*N*-methyl-amino]acetic acid



C25 H25 N O4; Mol wt: 403.4755

ACTION – Glycine uptake inhibitor that acts as an inhibitor of the glycine transporter GlyT1. Potentially useful for the treatment of mood disorders including depression, bipolar disorder, anxiety, panic, obsessive-compulsive disorder, stress disorders, schizophrenia, etc. Other exemplified compounds include the following:



Compound	R1	R2	Formula
314935	4-Cl-PhCO	H	C ₂₅ H ₂₄ Cl N O ₄
314936	4-Me-PhSO ₂	H	C ₂₅ H ₂₇ N O ₅ S
314937	3,4-(Cl)2-PhSO ₂	H	C ₂₄ H ₂₃ Cl ₂ N O ₅ S
314939	4-F-PhCO	H	C ₂₅ H ₂₄ F N O ₄
314940	2,4-(F)2-PhCO	F	C ₂₅ H ₂₂ F ₃ N O ₄
314941	4-MeO-PhCO	Cl	C ₂₆ H ₂₆ Cl N O ₅
314942	3,5-(CF ₃)2-PhCO	F	C ₂₇ H ₂₂ F ₇ N O ₄
314944	4-Pyr-CO	Cl	C ₂₄ H ₂₃ Cl N ₂ O ₄

SOURCE – Pfizer.

REFERENCES

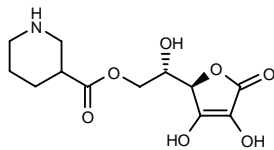
1. Lowe, J.A. III (Pfizer Products Inc.) *Benzophenones and sulfones as inhibitors of glycine uptake*. WO 0200602.

NEUROLOGIC DRUGS

ANTIEPILEPTIC DRUGS

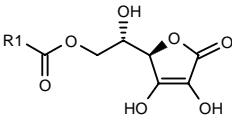
313870

6-O-(Piperidin-3-ylcarbonyl)-L-ascorbic acid



C12 H17 N O7; Mol wt: 287.2663

ACTION – Ascorbic acid and nipecotic acid conjugate able to interact with the Na⁺-dependent ascorbate transporter SVCT2 in human retinal pigment epithelial cells. In mice with pentylenetetrazol-induced convulsions, the conjugate significantly delayed the appearance of convulsions at a dose of 0.75 mmol/kg i.p., with no apparent toxicity and no lethality; nipecotic acid alone was ineffective. Potentially useful as an antiepileptic agent. Other related conjugates are:



Compound	R1	Formula
314203	2-[2,6-(Cl)2-PhNH]-PhCH ₂	C ₂₀ H ₁₇ Cl ₂ NO ₇
314204	4-OH-2-quinolyl	C ₁₆ H ₁₃ NO ₈

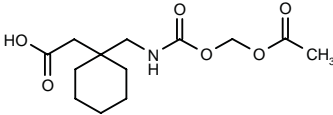
SOURCES – Università di Ferrara, Ferrara (IT); Medical College of Georgia, Augusta, GA (US).

REFERENCES

1. Manfredini, S. et al. *Design, synthesis and activity of ascorbic acid prodrugs of nipecotic, kynurenic and diclophenamic acids, liable to increase neurotropic activity*. J Med Chem 2002, 45(3): 559.

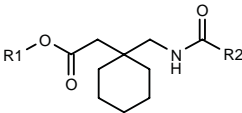
313894

2-[1-(Acetoxymethoxycarbonylaminomethyl)cyclohexyl]-acetic acid



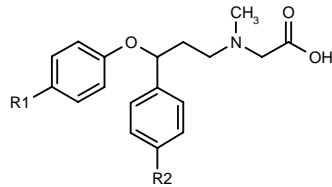
C13 H21 N O6; Mol wt: 287.3099

ACTION – A metabolically stable gabapentin analogue, useful in the treatment of epilepsy, faintness attacks, hypokinesia, cranial disorders, neurodegeneration, depression, anxiety, pain and panic, as well as neuro-pathological and digestive disorders. Other exemplified cyclic amino acid derivatives are:



Compound	R1	R2	Formula
313895	Et	OCH ₂ OAc	C ₁₅ H ₂₅ NO ₆
313896	H	t-BuCOOCH ₂ O	C ₁₆ H ₂₇ NO ₆
313897	Et	t-BuCOOCH ₂ O	C ₁₈ H ₃₁ NO ₆
313898	H	OCH ₂ OCOPh	C ₁₈ H ₂₃ NO ₆
313899	Et	OCH ₂ OCOPh	C ₂₀ H ₂₇ NO ₆
313900	H	Ph	C ₁₆ H ₂₁ NO ₃
313901	H	t-Bu	C ₁₄ H ₂₅ NO ₃
313902	H	CH ₂ Ph	C ₁₇ H ₂₃ NO ₃
313903	CH ₂ Ph	Ph	C ₂₃ H ₂₇ NO ₃
313904	Ph	Ph	C ₂₂ H ₂₅ NO ₃
313905	Et	Ph	C ₁₈ H ₂₅ NO ₃
313906	i-Pr	Ph	C ₁₉ H ₂₇ NO ₃
313907	CH ₂ Ph	CH ₂ Ph	C ₂₄ H ₂₅ NO ₃
313908	CH ₂ Ph	t-Bu	C ₂₁ H ₃₁ NO ₃
313909	Et	2-(PhCOOCH ₂)-Ph	C ₂₆ H ₃₁ NO ₅

ACTION – Glycine uptake inhibitor that acts as an inhibitor of the glycine transporter GlyT1. Potentially useful for the treatment of mood disorders including depression, bipolar disorder, anxiety, panic, obsessive-compulsive disorder, stress disorders, schizophrenia, etc. Other exemplified compounds include the following:



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314937	3,4-(Cl)2-PhSO ₂	H	C ₂₄ H ₂₃ Cl ₂ N O ₅ S
314939	4-F-PhCO	H	C ₂₅ H ₂₄ F N O ₄
314940	2,4-(F)2-PhCO	F	C ₂₅ H ₂₂ F ₃ N O ₄
314941	4-MeO-PhCO	Cl	C ₂₆ H ₂₆ Cl N O ₅
314942	3,5-(CF ₃)2-PhCO	F	C ₂₇ H ₂₂ F ₇ N O ₄
314944	4-Pyr-CO	Cl	C ₂₄ H ₂₃ Cl N ₂ O ₄

SOURCE – Pfizer.

REFERENCES

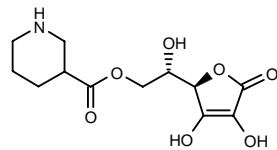
1. Lowe, J.A. III (Pfizer Products Inc.) *Benzophenones and sulfones as inhibitors of glycine uptake*. WO 0200602.

NEUROLOGIC DRUGS

ANTIEPILEPTIC DRUGS

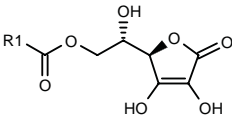
313870

6-O-(Piperidin-3-ylcarbonyl)-L-ascorbic acid



C12 H17 N O7; Mol wt: 287.2663

ACTION – Ascorbic acid and nipecotic acid conjugate able to interact with the Na⁺-dependent ascorbate transporter SVCT2 in human retinal pigment epithelial cells. In mice with pentylenetetrazol-induced convulsions, the conjugate significantly delayed the appearance of convulsions at a dose of 0.75 mmol/kg i.p., with no apparent toxicity and no lethality; nipecotic acid alone was ineffective. Potentially useful as an antiepileptic agent. Other related conjugates are:



Compound	R1	Formula
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314204	4-OH-2-quinolyl	C ₁₆ H ₁₃ NO ₈

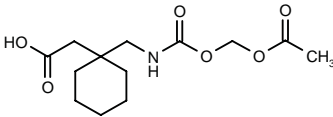
SOURCES – Università di Ferrara, Ferrara (IT); Medical College of Georgia, Augusta, GA (US).

REFERENCES

1. Manfredini, S. et al. *Design, synthesis and activity of ascorbic acid prodrugs of nipecotic, kynurenic and diclophenamic acids, liable to increase neurotropic activity*. J Med Chem 2002, 45(3): 559.

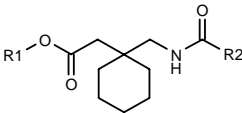
313894

2-[1-(Acetoxymethoxycarbonylaminomethyl)cyclohexyl]-acetic acid



C13 H21 N O6; Mol wt: 287.3099

ACTION – A metabolically stable gabapentin analogue, useful in the treatment of epilepsy, faintness attacks, hypokinesia, cranial disorders, neurodegeneration, depression, anxiety, pain and panic, as well as neuro-pathological and digestive disorders. Other exemplified cyclic amino acid derivatives are:



Compound	R1	R2	Formula
313895	Et	OCH ₂ OAc	C ₁₅ H ₂₅ NO ₆
313896	H	t-BuCOOCH ₂ O	C ₁₆ H ₂₇ NO ₆
313897	Et	t-BuCOOCH ₂ O	C ₁₈ H ₃₁ NO ₆
313898	H	OCH ₂ OCOPh	C ₁₈ H ₂₃ NO ₆
313899	Et	OCH ₂ OCOPh	C ₂₀ H ₂₇ NO ₆
313900	H	Ph	C ₁₆ H ₂₁ NO ₃
313901	H	t-Bu	C ₁₄ H ₂₅ NO ₃
313902	H	CH ₂ Ph	C ₁₇ H ₂₃ NO ₃
313903	CH ₂ Ph	Ph	C ₂₃ H ₂₇ NO ₃
313904	Ph	Ph	C ₂₂ H ₂₅ NO ₃
313905	Et	Ph	C ₁₈ H ₂₅ NO ₃
313906	i-Pr	Ph	C ₁₉ H ₂₇ NO ₃
313907	CH ₂ Ph	CH ₂ Ph	C ₂₄ H ₂₅ NO ₃
313908	CH ₂ Ph	t-Bu	C ₂₁ H ₃₁ NO ₃
313909	Et	2-(PhCOOCH ₂)-Ph	C ₂₆ H ₃₁ NO ₅

SOURCE – Pfizer.

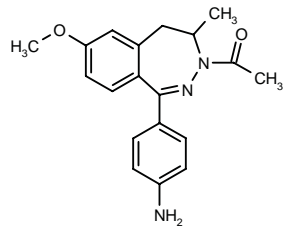
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1. Bryans, J.S. et al. (Pfizer Inc.) *Cyclic amino acid derivs. useful as pharmaceutical agents*. WO 0190052.

SYM-2267

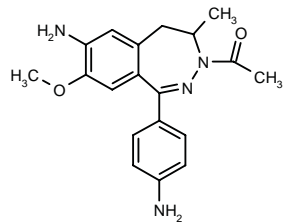
314680

4-(3-Acetyl-7-methoxy-4-methyl-4,5-dihydro-3H-2,3-benzodiazepin-1-yl)phenylamine



C19 H21 N3 O2; Mol wt: 323.3939

ACTION – AMPA receptor antagonist shown to inhibit AMPA-stimulated Ca²⁺ influx in cortical cells with an IC₅₀ of 26.1 μM and to display anticonvulsant activity with an oral ED₅₀ of 8.4 mg/kg in the rat maximal electroshock (MES) seizure model. Potentially useful for the treatment of neurological, neuropsychological, neuropsychiatric and neurodegenerative disorders such as seizures, depression, anxiety and drug abuse. Another exemplified 4,5-dihydro-3H-2,3-benzodiazepine is:



SYM-2269 [314682]: C19 H22 N4 O2

SOURCE – Annovis.

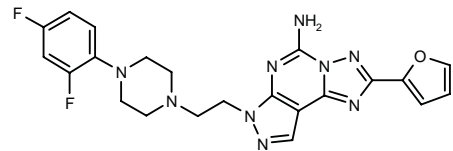
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1. Pei, X.-F. et al. (Annovis, Inc.) *5H-2,3-Benzodiazepine antagonists of excitatory amino acid receptors*. WO 0198280.

TREATMENT OF EXTRAPYRAMIDAL MOVEMENT DISORDERS

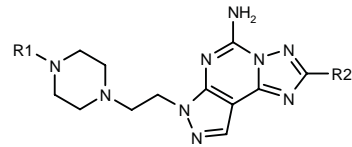
314056

7-[2-[4-(2,4-Difluorophenyl)piperazin-1-yl]ethyl]-2-(2-furyl)-7H-pyrazolo[4,3-e][1,2,4]triazolo[1,5-c]pyrimidin-5-amine



C22 H21 F2 N9 O; Mol wt: 465.4659

ACTION – Adenosine A_{2A} receptor antagonist, potentially useful for the treatment of Parkinson's disease, as well as depression, cognitive diseases, neurodegeneration and stroke. Other specifically claimed pyrazolo[4,3-e][1,2,4]-triazolo[1,5-c]pyrimidine derivatives are:



Compound	R1	R2	Formula
314057	Ph	2-furyl	C ₂₂ H ₂₃ N ₉ O
314058	2,4,6-(F)3-Ph	2-furyl	C ₂₂ H ₂₀ F ₃ N ₉ O
314059	4-(MeOCH2CH2O)-Ph	2-furyl	C ₂₈ H ₂₉ N ₉ O ₃
314060	2-F-4-(MeOCH2CH2O)-Ph	2-furyl	C ₂₈ H ₂₈ FN ₉ O ₃
314061	2-F-4,5-(MeO)2-Ph	2-furyl	C ₂₄ H ₂₆ FN ₉ O ₃
314062	2-F-4-Cl-Ph	2-furyl	C ₂₂ H ₂₁ ClFN ₉ O
314063	2,6-(F)2-4-(MeOCH2CH2O)-Ph	2-furyl	C ₂₈ H ₂₇ F ₂ N ₉ O ₃
314064	5-F-2-pyrimidinyl	2-furyl	C ₂₀ H ₂₀ FN ₁₁ O
314065	5-Me-2-Pyr	2-furyl	C ₂₂ H ₂₄ N ₁₀ O
314066	2,4-(F)2-Ph	3-F-Ph	C ₂₄ H ₂₂ F ₃ N ₉
314067	2,4-(F)2-Ph	Ph	C ₂₄ H ₂₃ F ₂ N ₉

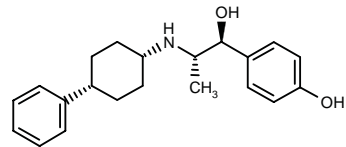
SOURCE – Schering-Plough.

REFERENCES

1. Neustadt, B.R. et al. (Schering Corp.) *Adenosine A_{2A} receptor antagonists*. WO 0192264.

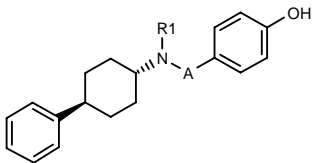
314116

cis-4-[1(S)-Hydroxy-2(S)-(4-phenylcyclohexylamino)propyl]phenol

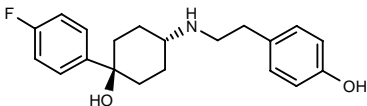


C21 H27 N O2; Mol wt: 325.4493

ACTION – NMDA receptor antagonist shown to inhibit [³H]-ifenprodil binding to NMDA receptors in rat brain preparations with an IC₅₀ value of 0.045 μM; in a similar assay, it gave an IC₅₀ of 0.15 μM at NR1A/NR2B NMDA receptor subtypes expressed in *Xenopus* oocytes. Compound demonstrated activity in a rat model of Parkinson's disease following oral administration. Other specifically claimed cyclohexylamines are:



Compound	R1	A	Formula
314117	H	-(S,S)-CH(OH)CH(Me)-	C ₂₁ H ₂₇ NO ₂
314118	H	-(CH2)3-	C ₂₁ H ₂₇ NO
314120	Me	-(CH2)3-	C ₂₂ H ₂₉ NO
314121	H	-(CH2)2-	C ₂₀ H ₂₅ NO
314122	Me	-(CH2)2-	C ₂₁ H ₂₇ NO
314123	H	-(CH2)4-	C ₂₂ H ₂₉ NO
314124	Me	-(CH2)4-	C ₂₃ H ₃₁ NO



314119: C20 H24 F N O2

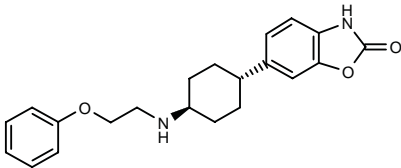
SOURCE – Pfizer.

REFERENCES

1. Deorazio, R.J. et al. (Pfizer Inc.) *Cyclohexylamine derivs. as subtype selective NMDA receptor antagonists*. WO 0192204.

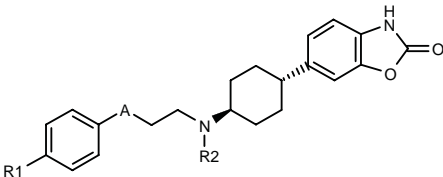
314125

trans-6-[4-(2-Phenoxyethylamino)cyclohexyl]benzoxazol-2(3*H*)-one



C21 H24 N2 O3; Mol wt: 352.4316

ACTION – NMDA receptor antagonist shown to inhibit [³H]-ifenprodil binding to NMDA receptors in rat brain preparations with an IC₅₀ value of 0.034 μM; in a similar assay, it gave an IC₅₀ of 0.10 μM at NR1A/NR2B NMDA receptor subtypes expressed in *Xenopus* oocytes. Compound demonstrated activity in a rat model of Parkinson's disease following oral administration. Other exemplified cyclohexylamines are:



Compound	R1	R2	A	Formula
314126	H	H	CH2	C ₂₂ H ₂₆ N ₂ O ₂
314127	F	H	O	C ₂₁ H ₂₃ FN ₂ O ₃
314128	F	Me	CH2	C ₂₃ H ₂₇ FN ₂ O ₂

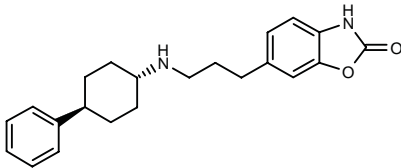
SOURCE – Pfizer.

REFERENCES

1. Nikam, S.S. et al. (Pfizer Inc.) *Bicyclic cyclohexylamines and their use as NMDA receptor antagonists*. WO 0192239.

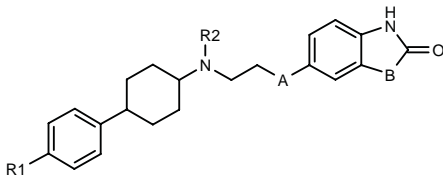
314292

trans-6-[3-(4-Phenylcyclohexylamino)propyl]benzoxazol-2(3*H*)-one



C22 H26 N2 O2; Mol wt: 350.4594

ACTION – Agent for the treatment of Parkinson's disease that acts as an NMDA receptor antagonist. It inhibited [³H]-ifenprodil binding to NMDA receptors in rat brain preparations with an IC₅₀ of 0.053 μM. Other exemplified bicyclic cyclohexylamines are:



Compound	R1	R2	A	B	Isomer	Formula
314293	F	H	CH2	O	trans	C ₂₂ H ₂₅ FN ₂ O ₂
314294	H	H	N(Me)	O	trans	C ₂₂ H ₂₇ N ₃ O ₂
314295	H	H	S	O	trans	C ₂₁ H ₂₄ N ₂ O ₂ S
314297	H	Me	bond	NH	trans	C ₂₂ H ₂₇ N ₃ O ₂
314299	F	Me	CH2	O	trans	C ₂₃ H ₂₇ FN ₂ O ₂
314300	F	Et	CH2	O	trans	C ₂₄ H ₂₉ FN ₂ O ₂
314301	H	H	O	NH	cis	C ₂₁ H ₂₅ N ₃ O ₂
314302	H	H	O	NH	trans	C ₂₁ H ₂₅ N ₃ O ₂

SOURCE – Pfizer.

REFERENCES

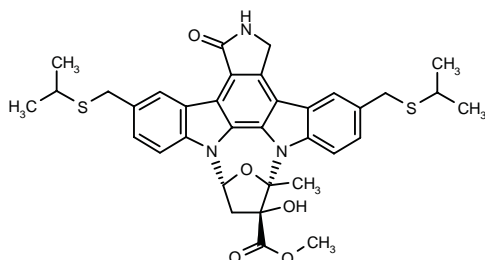
1. Deorazio, R.J. et al. (Pfizer Inc.) *Bicyclic cyclohexylamines and their use as NMDA receptor antagonists*. WO 0194321.

CEP-11004

314232

(9 α ,10 β ,12 α)-5,16-Bis(isopropylsulfanylmethyl)-9,12-epoxy-10-hydroxy-9-methyl-1-oxo-2,3,9,10,11,12-hexahydro-1*H*-diindolo[1,2,3-*fg*:3',2',1'-*k*]pyrrolo[3,4-*l*]-[1,6]benzodiazocine-10-carboxylic acid methyl ester

KT-8138



C35 H37 N3 O5 S2; Mol wt: 643.8253

ACTION – Mixed-lineage kinase (MLK) inhibitor (IC₅₀ = 45, 89 and 31 nM against MLK1, MLK2 and MLK3, respectively) with high selectivity over protein kinase C (PKC; IC₅₀ = 980 nM) and TrkA (IC₅₀ > 10,000 nM). Compound exhibited neuroprotective activity (40-100% at concentrations of 30-1000 nM) in several *in vitro* models of apoptotic cell death, including neuronally differentiated rat pheochromocytoma PC-12 cells following withdrawal of nerve growth factor (NGF), primary embryonic rat cortical neurons exposed to the amyloidogenic peptide A β 1-42 and retinoic acid-differentiated human SH-SY5Y cells treated with MPP⁺. In a model of MPTP-induced neurotoxicity in mice, compound at 1-10 mg/kg s.c. attenuated MPTP-mediated loss of nigrostriatal dopaminergic neurons and significantly suppressed the increase in phospho-MKK4 in the substantia nigra. Potentially useful for the treatment of neurodegenerative diseases such as Parkinson's disease, Huntington's disease and Alzheimer's disease.

SOURCES – Cephalon; Kyowa Hakko.

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TREATMENT OF IMMUNOLOGIC NEUROMUSCULAR DISORDERS

315048

Cyclo(L-valyl-L-histidyl-L-phenylalanyl-L-phenylalanyl-L-arginyl-L-asparaginyll-L-isoleucyl-L-valyl-L-threonyl-L-alanyl-L-arginyl-L-threonyl-L-prolyl)

C72 H110 N22 O16; Mol wt: 1539.7990

ACTION – Altered peptide ligand (APL), an analogue of human cyclic myelin basic protein MBP₈₇₋₈₉ proven to completely block the development of experimental allergic encephalomyelitis induced by guinea pig MBP₇₂₋₈₅ in rats. Moreover, compound induced the proliferation of human peripheral blood T-cells. Potentially useful for the treatment of multiple sclerosis.

SOURCES – Austin Research Institute, Melbourne (AU); Institut Pasteur, Paris (FR); National Hellenic Research Foundation, Athens (GR); National Institute of Chemistry, Ljubljana, Ljubljana (SI); University of Patras, Patras (GR).

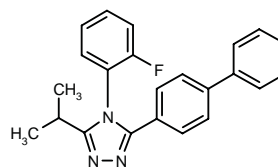
REFERENCES

- Tselios, T. et al. *Antagonistic effects of human cyclic MBP87-89 altered peptide ligands in experimental allergic encephalomyelitis and human T-cell proliferation*. J Med Chem 2002, 45(2): 275.

TREATMENT OF COGNITION DISORDERS

313176

3-(4-Biphenyl)-4-(2-fluorophenyl)-5-isopropyl-4*H*-1,2,4-triazole



C23 H20 F N3; Mol wt: 357.4300

ACTION – A representative compound from a series of triazole derivatives that act as inhibitors of glycine transporters. Compound gave an IC₅₀ of 0.36 μ M against the GlyT1 glycine transporter expressed in C6 glioma cells. *In vivo*, it was shown to attenuate the (+)-HA-166-induced increase in motor activity in mice by 57% at 10 mg/kg p.o. It also demonstrated activity against (+)-HA-966- and electroshock-induced learning impairment in mice, with a minimum effective dose (MED) of 3 and 10 mg/kg i.p., respectively. Expected to be useful for the treatment of dementia, schizophrenia and cognition disorders including Alzheimer's disease, Parkinson's disease and Huntington's chorea, as well as in the treatment of spasticity associated with neurodegenerative diseases and cerebrovascular disorders.

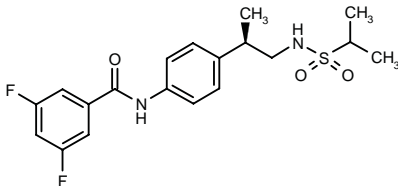
SOURCES – Merck KGaA; Yamanouchi.

REFERENCES

1. Tobe, T. et al. (Merck Patent GmbH;Yamanouchi Pharmaceutical Co., Ltd.) *Triazole derivs.* WO 0187855.

313553

3,5-Difluoro-*N*-[4-[2-(isopropylsulfonamido)-1(*R*)-methylethyl]phenyl]benzamide



C19 H22 F2 N2 O3 S; Mol wt: 396.4558

ACTION – Glutamate receptor potentiator from a series of sulfonamide derivatives, potentially useful for the treatment of Alzheimer's disease, depression, schizophrenia and obesity.

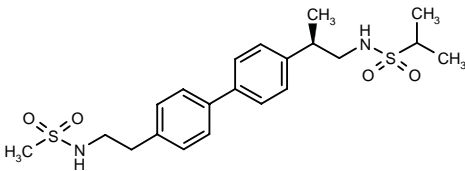
SOURCE – Lilly.

REFERENCES

1. Aikins, J.A. et al. (Eli Lilly and Company) *Sulfonamide derivs.* WO 0190056.
2. Skolnick, P. (Eli Lilly and Company) *Method of treating obesity.* WO 0189510.

313554

N-[2(*R*)-[4'-[2-(Methylsulfonamido)ethyl]biphenyl-4-yl]-propyl]propane-2-sulfonamide



C21 H30 N2 O4 S2; Mol wt: 438.6100

ACTION – Glutamate receptor potentiator from a series of sulfonamide derivatives, potentially useful for the treatment of Alzheimer's disease, depression, schizophrenia and obesity.

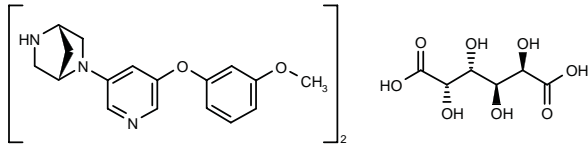
SOURCE – Lilly.

REFERENCES

1. Arnold, M.B. et al. (Eli Lilly and Company) *Sulfonamide derivs.* WO 0190057.
2. Skolnick, P. (Eli Lilly and Company) *Method of treating obesity.* WO 0189510.

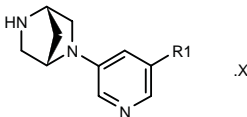
313639

(1*S*,4*S*)-2-[5-(3-Methoxyphenoxy)pyridin-3-yl]-2,5-diazabicyclo[2.2.1]heptane hemigalactarate

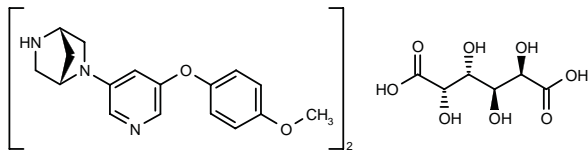


2 C17 H19 N3 O2 . C6 H10 O8; Mol wt: 804.8492

ACTION – Agent with the ability to activate nicotinic acetylcholine receptors ($K_i = 4 \text{ nM}$), potentially useful for the treatment of CNS disorders including Alzheimer's disease, HIV-related dementia, multiple cerebral infarcts, Parkinson's disease, Pick's disease, Huntington's chorea, tardive dyskinesia, hyperkinesia, attention deficit disorder, anxiety, depression, mild cognitive impairment and schizophrenia. Further applications include the treatment of pain, ulcerative colitis, inflammatory and autoimmune diseases, epilepsy, syphilis and Creutzfeldt-Jakob disease. Other exemplified diazabicyclic compounds are:



Compound	R1	X	Formula
313642	4-F-PhO	2HCl	C ₁₆ H ₁₆ FN ₃ O.2HCl
313643	3-thienyl		C ₁₄ H ₁₅ N ₃ S
313645	COPh	2HCl	C ₁₇ H ₁₇ N ₃ O.2HCl



313641: 2 C17 H19 N3 O2 . C6 H10 O8

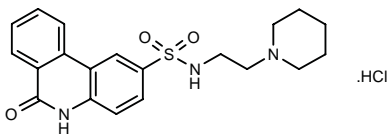
SOURCE – Targacept.

REFERENCES

1. Miller, C.H. et al. (Targacept, Inc.) *Heteroaryldiazabicycloalkanes as nicotinic cholinergic receptor ligands.* WO 0190109.

313678

6-Oxo-*N*-[2-(1-piperidiny)ethyl]-5,6-dihydrophenanthridine-2-sulfonamide hydrochloride



C20 H23 N3 O3 S . HCl; Mol wt: 421.9466

ACTION – A representative compound from a series of 5,6-dihydrophenanthridin-6-ones that acts as a poly(ADP-ribose)polymerase (PARP, NAD⁺ ADP-ribosyl-transferase) inhibitor (IC₅₀ = 0.01 μM). Potentially useful for the treatment of Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, cancer, gout and cardiovascular disorders such as cardiovascular tissue damage, coronary artery disease, myocardial infarction, angina pectoris and cardiogenic shock.

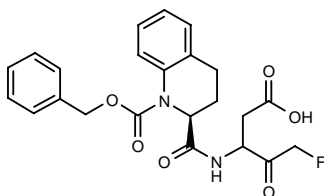
SOURCE – Guilford.

REFERENCES

1. Li, J.-H. et al. (Guilford Pharmaceuticals Inc.) *Sulfonamide and carbamide derivs. of 6(5H)phenanthridinones and their uses.* WO 0190077.

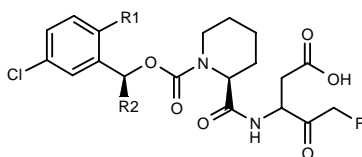
313728

3-[1-(Benzyloxycarbonyl)-1,2,3,4-tetrahydroquinolin-2(S)-ylcarboxamido]-5-fluoro-4-oxopentanoic acid



C23 H23 F N2 O6; Mol wt: 442.4407

ACTION – Peptidomimetic caspase inhibitor active *in vitro* against caspases 1, 3 and 8. It inhibited lipopolysaccharide-induced IL-1β secretion in human peripheral blood mononuclear cells with an IC₅₀ of 1150 nM. Potentially useful for the treatment of a broad range of IL-1- and apoptosis-mediated disorders such as inflammation, autoimmune diseases, destructive bone disorders, proliferative disorders, infections, asthma, diabetes, neurodegenerative disorders, etc., as well as for the treatment of complications associated with coronary artery bypass grafts and for the preservation of cells and blood products for use in transplantation. Other exemplified compounds are:



Compound	R1	R2	Formula
313730	H	H	C ₁₉ H ₂₂ ClFN ₂ O ₆
313731	H	CF ₃	C ₂₀ H ₂₁ ClF ₄ N ₂ O ₆
313732	Cl	H	C ₁₈ H ₂₁ Cl ₂ FN ₂ O ₆

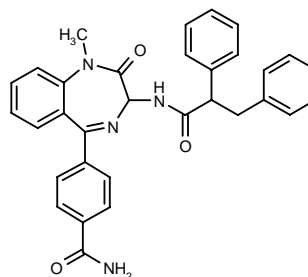
SOURCE – Vertex.

REFERENCES

1. Golec, J. (Vertex Pharmaceuticals Inc.) *Caspase inhibitors and uses thereof.* WO 0190070.

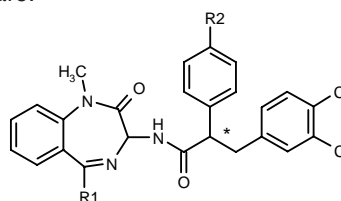
313841

(±)-4-[3-(2,3-Diphenylpropionamido)-1-methyl-2-oxo-2,3-dihydro-1H-1,4-benzodiazepin-5-yl]benzamide

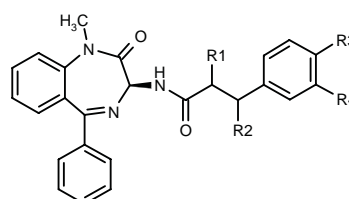


C32 H28 N4 O3; Mol wt: 516.5982

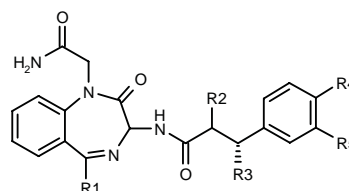
ACTION – Agent with the ability to inhibit the formation of β-amyloid peptide (Aβ) through inhibition of γ-secretase and therefore potentially useful for the treatment of conditions associated with Aβ deposition, particularly Alzheimer's disease. Other exemplified benzodiazepine derivatives are:



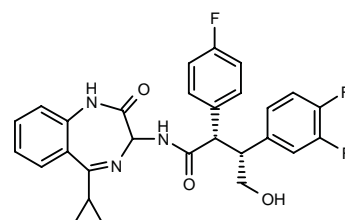
Compound	R1	R2	* Isomer	Formula
313842	4-Pyr	H		C ₃₀ H ₂₄ Cl ₂ N ₄ O ₂
313848	5-oxo-5,6,7,8-tetrahydro-2-Naph	F	R	C ₃₅ H ₂₈ Cl ₂ FN ₃ O ₃



Compound	R1	R2	R3=R4	Formula
313845	(R)-3-thienyl	H	Cl	C ₂₉ H ₂₃ Cl ₂ N ₃ O ₂ S
313846	Me	CH ₂ OH	F	C ₂₇ H ₂₆ F ₂ N ₃ O ₃



Compound	R1	R2	R3	R4=R5	Formula
313849	i-Pr	(R)-4-F-Ph	OH	Cl	C ₂₉ H ₂₇ Cl ₂ FN ₄ O ₄
313851	1,3-benzodioxol-5-yl	CF ₃	H	H	C ₂₈ H ₂₃ F ₃ N ₄ O ₅
313852	1,3-benzodioxol-5-yl	(R)-i-Pr	H	F	C ₃₀ H ₂₈ F ₂ N ₄ O ₅



313855: C28 H24 F3 N3 O3

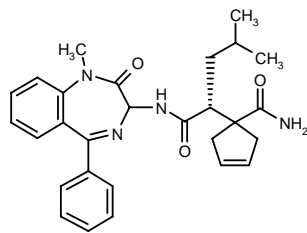
SOURCE – Merck Sharp & Dohme.

REFERENCES

1. Castro Pineiro, J.L. et al. (Merck Sharp & Dohme Ltd.) *Benzodiazepine derivs. as APP modulators*. WO 0190084.

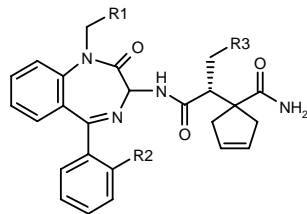
314006

1-[3-Methyl-1 (*R*)-[*N*-(1-methyl-2-oxo-5-phenyl-2,3-dihydro-1*H*-1,4-benzodiazepin-3-yl)carbamoyl]butyl]-3-cyclopentene-1-carboxamide

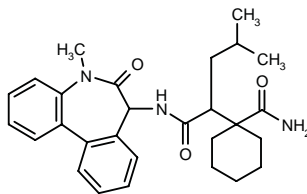


C28 H32 N4 O3; Mol wt: 472.5858

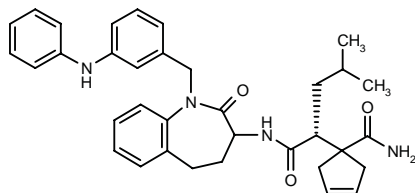
ACTION – Agent with the ability to inhibit the formation of β -amyloid peptide ($A\beta$) through inhibition of γ -secretase, potentially useful for the treatment of Alzheimer's disease. Other exempified lactams are:



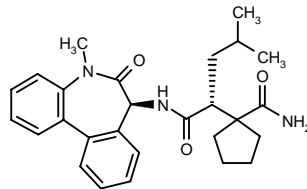
Compound	R1	R2	R3	Isomer	Formula
314011	H	CF3	cyclopropyl		C ₂₉ H ₂₉ F ₃ N ₄ O ₃
314014	cyclopropyl-CH2	F	i-Pr	3S	C ₃₂ H ₃₇ FN ₄ O ₃
314016	H	CF3	i-Pr		C ₂₉ H ₃₁ F ₃ N ₄ O ₃



314007: C28 H35 N3 O3



314009: C35 H40 N4 O3



314012: C27 H33 N3 O3

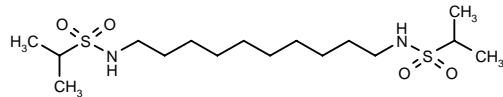
SOURCE – Bristol-Myers Squibb.

REFERENCES

1. Olson, R.E. (DuPont Pharmaceuticals Co.) *Lactams substd. by cyclic succinates as inhibitors of A β protein production*. WO 0192235.

314239

N,N'-(Decane-1,10-diyl)bis(isopropanesulfonamide)



C16 H36 N2 O4 S2; Mol wt: 384.6024

ACTION – A representative compound from a series of sulfonamide derivatives with the ability to potentiate glutamate receptors, particularly GluR4. Compound was active in the forced swimming test in mice with a minimum effective dose (MED) of 5 μ g/kg p.o. and is indicated for the treatment of cognition disorders such as Alzheimer's disease, as well as schizophrenia and depression.

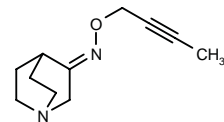
SOURCE – Lilly.

REFERENCES

1. Knobelsdorf, J.A. and Zarrinmayeh, H. (Eli Lilly and Company) *(Bis)sulfonamide derivs*. WO 0194306.

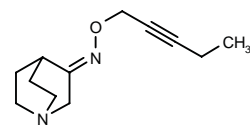
314320

Quinuclidin-3-one *O*-2-butyntyloxime



C11 H16 N2 O; Mol wt: 192.2604

ACTION – Muscarinic M₁ receptor agonist with submicromolar affinity for M₁, M₂ and M₃ receptors, as demonstrated by K_i values of 894, 218 and 464 μ M, respectively, for displacement of [³H]-pirenzepine binding in rat cortex, [³H]-*N*-methylscopolamine binding in rat heart and [³H]-*N*-methylscopolamine binding in rat submandibular gland. It protected mice from scopolamine-induced impairment in the swimming task. Potentially useful for the treatment of Alzheimer's disease. Another related compound is:



314321: C12 H18 N2 O

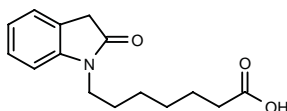
SOURCES – DSO National Laboratories; National University of Singapore (SG).

REFERENCES

1. Somanadhan, B. et al. *Quinuclidinone O-alkynyloximes with muscarinic agonist activity*. *Bioorg Med Chem* 2002, 10(1): 207.

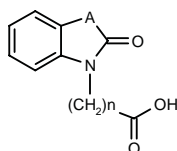
314523

7-(2-Oxo-2,3-dihydro-1*H*-indol-1-yl)heptanoic acid



C15 H19 N O3; Mol wt: 261.3191

ACTION – Cytoprotective agent with antiapoptotic activity in neuronal and renal cells. It inhibited β -amyloid peptide-induced apoptosis in rat cerebral cortex cells by 35% at 0.1 μ M and caused no deaths in acute toxicity tests in rats at 30 mg/kg p.o. Potentially useful for the treatment of neuropathies and neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, Huntington's chorea and amyotrophic lateral sclerosis, as well as nephropathies including nephritis, renal failure, glomerulonephritis and nephrotic syndrome. Other exemplified compounds are:



Compound	A	n	Formula
314524	CH ₂	5	C ₁₄ H ₁₇ NO ₃
314525	CH ₂	4	C ₁₃ H ₁₅ NO ₃
314526	CH ₂	7	C ₁₆ H ₂₁ NO ₃
314527	CH ₂	8	C ₁₇ H ₂₃ NO ₃
314568	S	6	C ₁₄ H ₁₇ NO ₃ S

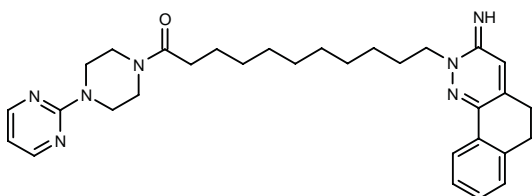
SOURCE – Mitsubishi Pharma.

REFERENCES

1. Ashimori, A. et al. (Wellfide Corp.) *Cytoprotectors*. WO 0194311.

314661

2-[11-Oxo-11-[4-(2-pyrimidinyl)piperazin-1-yl]undecyl]-2,3,5,6-tetrahydrobenzo[h]cinnolin-3-imine



C31 H41 N7 O; Mol wt: 527.7129

ACTION – Glial activation inhibitor proven to selectively block the production of IL-1 β , inducible nitric oxide synthase (iNOS) and NO by activated glia, while having no effect on the production of potentially beneficial antiinflammatory glial proteins, i.e., apolipoprotein E (apo E), or cyclooxygenase type 2 (COX-2). Compound selectively inhibited calmodulin-dependent kinase (CaMK; IC₅₀ = 9.7 μ M), but was inactive at up to 100 μ M against other protein kinases. Potentially useful for the treatment of neuroinflammation in degenerative disorders including Alzheimer's disease and stroke.

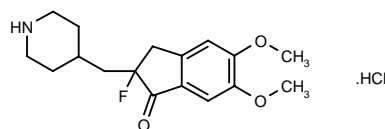
SOURCES – Université Louis Pasteur, Strasbourg (FR); Northwestern University, Evanston, IL (US).

REFERENCES

1. Mirzoeva, S. et al. *Discovery of a 3-amino-6-phenyl-pyridazine derivative as a new synthetic antineuroinflammatory compound*. *J Med Chem* 2002, 45(3): 563.

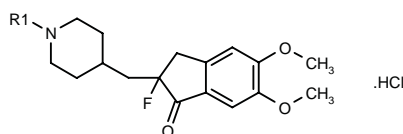
314830

2-Fluoro-5,6-dimethoxy-2-(piperidin-4-ylmethyl)indan-1-one hydrochloride



C17 H22 F N O3 . HCl; Mol wt: 343.8237

ACTION – Acetylcholinesterase inhibitor, potentially useful for the treatment of senile dementia, particularly Alzheimer's disease, cerebrovascular dementia and attention deficit hyperactivity disorder. Other exemplified 4-substituted piperidine derivatives include the following:



Compound	R1	Formula
314832	Me	C ₁₈ H ₂₄ FNO ₃ .HCl
314833	i-Pr	C ₂₀ H ₂₈ FNO ₃ .HCl
314834	i-Bu	C ₂₁ H ₃₀ FNO ₃ .HCl

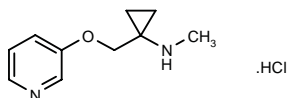
SOURCE – Eisai.

REFERENCES

1. Iimura, Y. and Kosasa, T. (Eisai Co., Ltd.) *4-Substd. piperidine cpd*. WO 0198271.

314918

N-Methyl-1-(pyridin-3-yloxymethyl)cyclopropanamine hydrochloride



C10 H14 N2 O . HCl; Mol wt: 214.6945

ACTION – A representative compound from a series of cyclopropyl-containing amines and carboxamides that acts as a selective ligand for nicotinic $\alpha 4\beta 2$ receptors. Potentially useful for the treatment of memory disorders associated with age and neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, Pick's disease, Korsakoff's syndrome and frontal and subcortical dementia, as well as for the treatment of mood disorders, Tourette syndrome, attention deficit hyperactivity disorder, pain and smoking cessation.

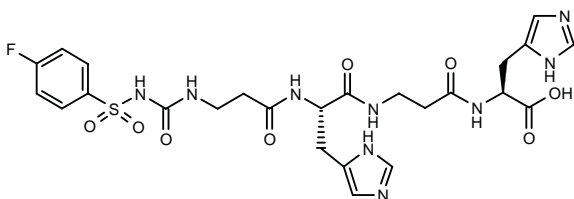
SOURCE – Servier.

REFERENCES

1. Goldstein, S. et al. (Servier Laboratoires) *1,1- And 1,2-disubst. cyclopropanes, process for their preparation and pharmaceutical compns. thereof*. EP 1170281, FR 2810664.

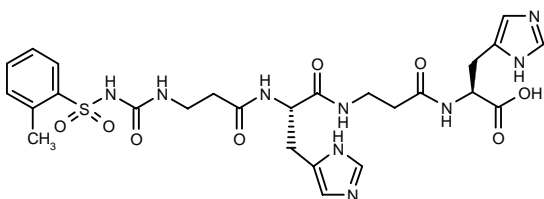
315045

N-(4-Fluorophenylsulfonamidocarbonyl)- β -alanyl-L-histidyl- β -alanyl-L-histidine



C25 H30 F N9 O8 S; Mol wt: 635.6310

ACTION – Tight-binding carbonic anhydrase (CA) activator ($K_A = 2, 5$ and 10 nM for human CA I, bovine CA IV and human CA II isozymes, respectively). In *ex vivo* experiments using human erythrocytes, compound showed high enhancement of CA activity (254 and 283% after 30- and 60-min incubation, respectively, at $5 \mu\text{M}$). Potentially useful for the treatment of CA deficiency syndrome, as well as for the treatment of cognitive diseases such as Alzheimer's disease. Another related compound is:



315046: C26 H33 N9 O8 S

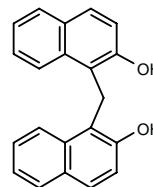
SOURCE – Università degli Studi di Firenze, Firenze (IT).

REFERENCES

1. Scozzafava, A. and Supuran, C.T. *Carbonic anhydrase activators: High affinity isozymes I, II, and IV activators, incorporating a β -alanyl-histidine Scaffold*. J Med Chem 2002, 45(2): 284.

ST-1859**314932**

1,1'-Methylenebis(naphthalen-2-ol)



C21 H16 O2; Mol wt: 300.3554

ACTION – Pamoic acid derivative with the ability to inhibit the formation of β -amyloid ($A\beta$) aggregates, shown to inhibit the polymerization of $A\beta(1-42)$ *in vitro* with an EC_{50} of $5.4 \mu\text{M}$. *In vivo*, compound was able to cross the blood-brain barrier following i.v. administration to rats. Potentially useful for the treatment of Alzheimer's disease, Down's syndrome, hereditary cerebral hemorrhage associated with Dutch-type amyloidosis, as well as amyloidosis associated with chronic inflammation, multiple myeloma, type 2 diabetes and prion diseases, particularly Creutzfeldt-Jakob disease and Gerstmann-Straussler syndrome.

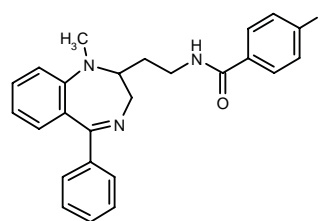
SOURCE – Sigma-Tau.

REFERENCES

1. Gallo, M.G. et al. (Sigma-Tau Industrie Farmaceutiche Riunite SpA) *Use of pamoic acid or one of its derivs., or one of its analogues, for the preparation of a medicament for the treatment of diseases characterised by deposits of amyloid aggregates*. WO 0200603.

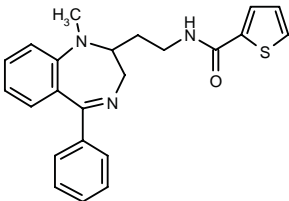
VA-100²⁻⁴**302135**

4-Fluoro-N-[2-(1-methyl-5-phenyl-2,3-dihydro-1H-1,4-benzodiazepin-2-yl)ethyl]benzamide



C25 H24 F N3 O; Mol wt: 401.4826

ACTION – Kappa opioid receptor agonist with subnano-molar affinity for the receptor ($K_i = 0.56$ nM) and selectivity over mu and delta opioid receptors ($K_i = 2.26$ and 275 nM, respectively). In a rat passive avoidance paradigm, compound (50-100 mg/kg p.o.) dose-dependently antagonized the amnesic effect of the kappa opioid receptor agonist *n*-binaltorphimine and completely prevented deficits induced by scopolamine, mecamlamine, diphenhydramine and baclofen. At the highest effective dose, it did not impair motor coordination in the rotarod test and did not modify spontaneous motility. Potentially useful as an antiamnesic agent. Another related compound is:



VA-101 [302137]:¹⁻⁴ C23 H23 N3 O S

SOURCES – Università degli Studi di Catanzaro, Catanzaro (IT); Università degli Studi di Firenze, Firenze (IT); Università degli Studi di Siena, Siena (IT).

REFERENCES

1. Azzolina, O. et al. *Enantiomers of 2-(acylamino)ethyl-1,4-benzodiazepines, potent ligands of kappa-opioid receptor: Chiral chromatographic resolution, configurational assignment and biological activity.* Chirality 2001, 13(9): 606.

2. Capelli, A. et al. *Synthesis, biological evaluation, and quantitative receptor docking simulations of 2-((acylamino)ethyl)-1,4-benzodiazepines as novel tifluadom-like ligands with high affinity and selectivity for kappa-opioid receptors.* J Med Chem 1996, 39(4): 860.

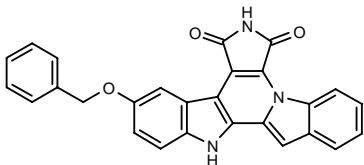
3. Cappelli, A. et al. *Antiamnesia effect of the two novel kappa opioid agonists: VA-100 and VA-101.* Soc Neurosci Abst 2000, 26(Part 1): Abst 342.11.

4. Ghelardini, C. et al. *Antiamnesic effect of the two novel kappa-opioid agonists, VA-100 and VA-101, in the mouse passive avoidance test.* Drug Dev Res 2001, 54(1): 12.

TREATMENT OF
CEREBROVASCULAR DISEASES

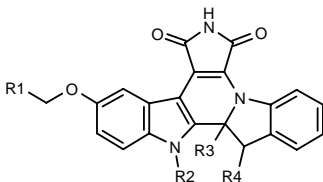
313319

10-(Benzyloxy)pyrrolo[3',4':5,6]pyrido[1,2-a:3,4-b']-diindole-6,8(7*H*,13*H*)-dione



C27 H17 N3 O3; Mol wt: 431.4493

ACTION– Neuroprotective and antiproliferative agent with the ability to induce apoptosis in proliferating cells and to inhibit neuronal apoptosis and/or axonal degradation. It inhibited cisplatin-induced apoptosis in cultured cortical neurons by 40% at 10 μ M. Potentially useful for the treatment of neurodegenerative diseases, inflammation and cancer. Other exemplified polycyclic compounds are:



Compound	R1	R2	R3	R4	Formula
313320	Ph	H	H	H	C ₂₇ H ₁₉ N ₃ O ₃
313321	Ph	CH2CH2OH	H	H	C ₂₉ H ₂₃ N ₃ O ₄
313322	H	COCH2OAc	bond		C ₂₅ H ₁₇ N ₃ O ₆

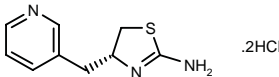
SOURCE – Aegea Therapeutics.

REFERENCES

1. Jaquith, J.B. et al. (Aegea Therapeutics Inc.) *Neuroprotective and anti-proliferative cpds.* WO 0187887.

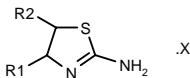
314391

(+)-4(*R*)-(Pyridin-3-ylmethyl)-4,5-dihydrothiazol-2-amine dihydrochloride



C9 H11 N3 S . 2HCl; Mol wt: 266.1947

ACTION – Agent with the ability to inhibit inducible nitric oxide synthase (iNOS), expected to be useful for the treatment of NO-mediated diseases including cerebral ischemia, brain and spinal cord trauma, Parkinson’s disease, Huntington’s disease, Alzheimer’s disease, amyotrophic lateral sclerosis, migraine, depression, schizophrenia, anxiety, epilepsy, diabetes, atherosclerosis, myocarditis, arthritis, asthma, irritable bowel syndrome, Crohn’s disease, psoriasis, cancer, bacterial infections, glomerulonephritis, lupus erythematosus, etc. Other exemplified 2-aminothiazoline derivatives include the following:



Compound	R1	R2	Isomer	X	Formula
314392	3-thienyl-CH2	H	(-)-R	HCl	C ₈ H ₁₀ N ₂ S ₂ .HCl
314393	3-NO2-PhCH2	H	(-)-S	HCl	C ₁₀ H ₁₁ N ₂ O ₂ S.HCl
314394	H	Me	(+)-S	HCl	C ₄ H ₈ N ₂ S.HCl
314395	4-Pyr-CH2	Me	(+)-4R,5R	2HCl	C ₁₀ H ₁₃ N ₃ S ₂ .2HCl
314397	4-thiazolyl-CH2	H	(+)-R	2HCl	C ₇ H ₉ N ₃ S ₂ .2HCl
314398	4-OH-PhCH2	H	(+)-R	HCl	C ₁₀ H ₁₂ N ₂ OS.HCl
314399	1-oxido-4-Pyr-CH2	H	R	HCl	C ₉ H ₁₁ N ₃ OS.HCl
314400	2-thienyl-CH2	H	R	HCl	C ₈ H ₁₀ N ₂ S ₂ .HCl

SOURCE – Aventis Pharma.

REFERENCES

1. Carry, J.-C. et al. (Aventis Pharma SA) *2-Aminothiazoline derivs. and their use as NO-synthase inhibitors.* FR 2810037, WO 0194325.

EMP-6

314068

Glycyl-glycyl-L-threonyl-L-alanyl-L-seryl-L-cysteinyl-L-histidyl-L-phenylalanyl-glycyl-L-prolyl-L-leucyl-L-threonyl-L-tryptophyl-L-valyl-L-cysteinyl-L-lysyl-L-prolyl-L-glutamyl-L-glycyl-glycine

C88 H131 N25 O25 S2; Mol wt: 2003.2850

ACTION – Peptide with affinity for erythropoietin (EPO) receptors and shown to promote neurite outgrowth in rat hippocampal and cortical cultures. Potentially useful for the treatment of acute and chronic neurodegenerative disorders such as cerebral ischemia, reperfusion following acute ischemia, cardiac arrest, intracranial hemorrhage, Alzheimer's disease, Pick's disease, progressive supranuclear palsy, multistem degeneration, epilepsy, Huntington's disease and Parkinson's disease.

SOURCE – Ortho-McNeil.

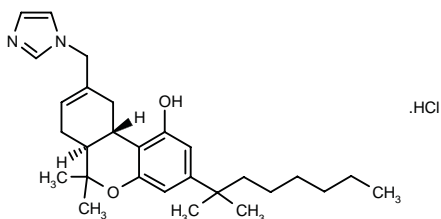
REFERENCES

1. Smith-Swintosky, V. et al. (Ortho-McNeil Pharmaceutical, Inc.) *Neuroprotective peptides*. WO 0191780.

PRS-211095

310971

(6a*S*,10a*S*)-3-(1,1-Dimethylheptyl)-9-(1*H*-imidazol-1-ylmethyl)-6,6-dimethyl-6a,7,10,10a-tetrahydro-6*H*-dibenzo[*b,d*]pyran-1-ol hydrochloride



C28 H40 N2 O2 . HCl; Mol wt: 473.0969

ACTION – Dexanabinol derivative with 5-fold improved affinity for the NMDA receptor and 2-fold higher inhibitory activity against cyclooxygenase type 2 (COX-2) compared to the parent compound. In a focal cerebral ischemia model in rats induced by occlusion of the middle cerebral artery for 120 min, compound (0.5-10 mg/kg i.v.) dose - dependently improved (40-80%) both sensory and motor skills; infarct volume was reduced at all doses, with a 35% decrease on 5 mg/kg.

SOURCE – Pharmos.

REFERENCES

1. Garzon, A. and Fink, G. (Pharmos Corp.) *Novel non-psychotropic cannabinoids*. WO 0198289.

2. Bar-Joseph, A. et al. *Neuroprotection by new dexanabinol analogs in a transient middle cerebral artery (MCA) occlusion in rats*. 9th Annu Meet Isr Soc Neurosci (Dec 3-6, Eilat) 2000, Abst.

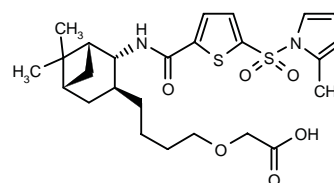
3. Bar-Joseph, A. et al. *Neuroprotection by PRS-211,095: Assessed functionally and morphologically in transient MCA occlusion in rats*. Soc Neurosci Abst 2001, 27 Abst 209.5.

RESPIRATORY DRUGS

ASTHMA THERAPY

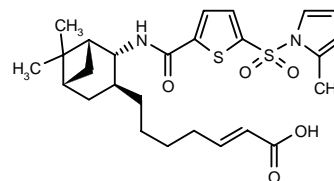
313866

2-[4-[(1*R*,2*R*,3*S*,5*S*)-6,6-Dimethyl-2-[5-(2-methyl-1*H*-pyrrol-1-ylsulfonyl)thien-2-ylcarboxamido]bicyclo[3.1.1]-hept-3-yl]butoxy]acetic acid



C25 H34 N2 O6 S2; Mol wt: 522.6836

ACTION – Dual TxA₂ and PGD₂ antagonist proven to inhibit [³H]-PGD₂ binding in human platelet membrane fractions (IC₅₀ = 0.0013 μM) and the PGD₂-induced increase in human platelet cAMP levels (IC₅₀ = 0.013 μM); it gave an IC₅₀ of 0.0022 μM when tested for TxA₂-antagonist activity and was active in inhibiting antigen-induced nasal obstruction in sensitized guinea pigs. Another exemplified compound is:



313868: C26 H34 N2 O5 S2

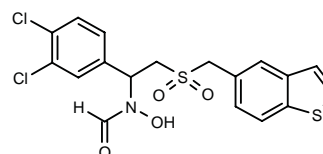
SOURCE – Shionogi.

REFERENCES

1. Tanimoto, N. and Arimura, A. (Shionogi & Co. Ltd.) *Drug compsn. antagonistic to both PGD₂/TXA₂ receptors*. WO 0194309.

313910

N-[2-(1-Benzothien-5-ylmethylsulfonyl)-1-(3,4-dichlorophenyl)ethyl]-N-hydroxyformamide



C18 H15 Cl2 N O4 S2; Mol wt: 444.3575

EMP-6

314068

Glycyl-glycyl-L-threonyl-L-alanyl-L-seryl-L-cysteinyl-L-histidyl-L-phenylalanyl-glycyl-L-prolyl-L-leucyl-L-threonyl-L-tryptophyl-L-valyl-L-cysteinyl-L-lysyl-L-prolyl-L-glutamyl-L-glycyl-glycine

C88 H131 N25 O25 S2; Mol wt: 2003.2850

ACTION – Peptide with affinity for erythropoietin (EPO) receptors and shown to promote neurite outgrowth in rat hippocampal and cortical cultures. Potentially useful for the treatment of acute and chronic neurodegenerative disorders such as cerebral ischemia, reperfusion following acute ischemia, cardiac arrest, intracranial hemorrhage, Alzheimer's disease, Pick's disease, progressive supranuclear palsy, multistem degeneration, epilepsy, Huntington's disease and Parkinson's disease.

SOURCE – Ortho-McNeil.

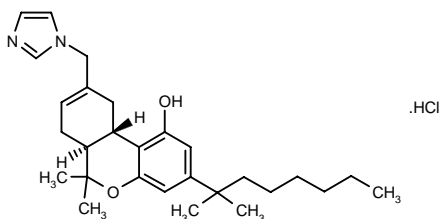
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PRS-211095

310971

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C28 H40 N2 O2 . HCl; Mol wt: 473.0969

ACTION – Dexanabinol derivative with 5-fold improved affinity for the NMDA receptor and 2-fold higher inhibitory activity against cyclooxygenase type 2 (COX-2) compared to the parent compound. In a focal cerebral ischemia model in rats induced by occlusion of the middle cerebral artery for 120 min, compound (0.5-10 mg/kg i.v.) dose - dependently improved (40-80%) both sensory and motor skills; infarct volume was reduced at all doses, with a 35% decrease on 5 mg/kg.

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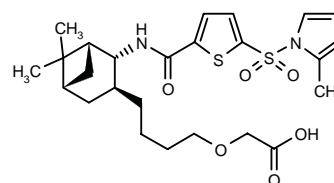
3. Bar-Joseph, A. et al. *Neuroprotection by PRS-211,095: Assessed functionally and morphologically in transient MCA occlusion in rats*. Soc Neurosci Abst 2001, 27 Abst 209.5.

RESPIRATORY DRUGS

ASTHMA THERAPY

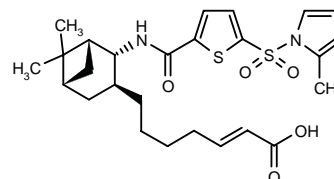
313866

2-[4-[(1*R*,2*R*,3*S*,5*S*)-6,6-Dimethyl-2-[5-(2-methyl-1*H*-pyrrol-1-ylsulfonyl)thien-2-ylcarboxamido]bicyclo[3.1.1]-hept-3-yl]butoxy]acetic acid



C25 H34 N2 O6 S2; Mol wt: 522.6836

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313868: C26 H34 N2 O5 S2

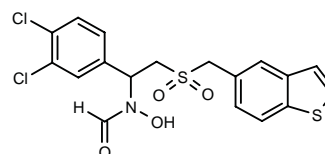
SOURCE – Shionogi.

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1. Tanimoto, N. and Arimura, A. (Shionogi & Co. Ltd.) *Drug compsn. antagonistic to both PGD₂/TXA₂ receptors*. WO 0194309.

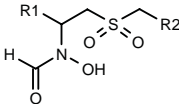
313910

N-[2-(1-Benzothien-5-ylmethylsulfonyl)-1-(3,4-dichlorophenyl)ethyl]-N-hydroxyformamide



C18 H15 Cl2 N O4 S2; Mol wt: 444.3575

ACTION – Agent with the ability to inhibit the formation of soluble human CD23 (sCD23) and the processing of TNF. It inhibited the production of sCD23 in membranes of RPMI 8866 cells with an IC₅₀ < 1 μM, while displaying IC₅₀ values > 10 μM against collagenase. Potentially useful for the treatment of allergy, asthma, atopic dermatitis, inflammation, autoimmune diseases, Alzheimer’s disease, multiple sclerosis, multiinfarct dementia, fever, hemorrhage, cachexia, anorexia, acute infections and transplant rejection, among others. Other exemplified sulfonyl-containing *N*-hydroxyformamide derivatives include the following:



Compound	R1	R2	Isomer	Formula
313911	Ph	5-benzothieryl		C ₁₈ H ₁₇ NO ₄ S ₂
313912	4-MeO-Ph	5-benzothieryl		C ₁₉ H ₁₉ NO ₅ S ₂
313913	1,4-benzodioxan-6-yl	5-benzothieryl		C ₂₀ H ₁₉ NO ₆ S ₂
313914	3,4-dihydro-2H-1,5-benzodioxepin-7-yl	5-benzothieryl		C ₂₁ H ₂₁ NO ₆ S ₂
313916	3-MeO-Ph	5-benzothieryl	S	C ₁₉ H ₁₉ NO ₅ S ₂
313917	3-F-Ph	5-benzothieryl	S	C ₁₈ H ₁₆ FNO ₄ S ₂
313918	4-F-Ph	5-benzothieryl	S	C ₁₈ H ₁₆ FNO ₄ S ₂
313919	Ph	2-indanyl	S	C ₁₉ H ₂₁ NO ₄ S
313920	Ph	5-benzofuryl	S	C ₁₈ H ₁₇ NO ₅ S
313921	Ph	2-F-5-benzothieryl	S	C ₁₈ H ₁₆ FNO ₄ S ₂
313923	Ph	3-quinolyl	S	C ₁₉ H ₁₈ N ₂ O ₄ S
313924	4-(AcNH)-Ph	5-benzothieryl	S	C ₂₀ H ₂₀ N ₂ O ₅ S ₂
313925	4-CO ₂ Et-Ph	3-quinolyl	S	C ₂₂ H ₂₂ N ₂ O ₆ S
313927	Ph	thieno[2,3- <i>b</i>]pyridin-5-yl	S	C ₁₇ H ₁₆ N ₂ O ₄ S ₂
313928	Ph	thieno[3,2- <i>b</i>]pyridin-6-yl	S	C ₁₇ H ₁₆ N ₂ O ₄ S ₂
313929	4-MeO-Ph	3-quinolyl	S	C ₂₀ H ₂₀ N ₂ O ₅ S
313930	i-Bu	3-quinolyl	S	C ₁₇ H ₂₂ N ₂ O ₄ S
313931	i-PrOCH ₂	5-benzothieryl	S	C ₁₆ H ₂₁ NO ₅ S ₂

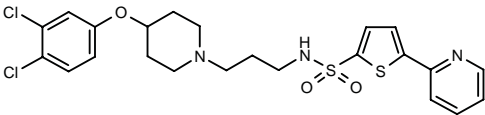
SOURCE – GlaxoSmithKline.

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1. Best, D.J. et al. (GlaxoSmithKline plc) *Bicycyl or heterobicycylmethanesulfonyl-amino-substd. N-hydroxyformamides*. WO 0190100.

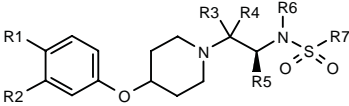
314095

N-[3-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]propyl]-5-(2-pyridyl)thiophene-2-sulfonamide

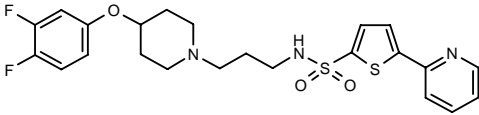


C23 H25 Cl2 N3 O3 S2; Mol wt: 526.5065

ACTION – Modulator of chemokine receptors, particularly CCR3, considered to have potential in the treatment of autoimmune, inflammatory, proliferative and immunologically mediated diseases, particularly asthma or rhinitis. Other exemplified piperidine derivatives include the following:



Compound	R1=R2	R3	R4	R5	R6	R7	Formula
314097	F	H	H	H	H	5-(2-Pyr)-2-thienyl	C ₂₂ H ₂₃ F ₂ N ₃ O ₃ S ₂
314098	F	-O-	CH2Ph	H	H	5-(2-Pyr)-2-thienyl	C ₂₉ H ₂₇ F ₂ N ₃ O ₄ S ₂
314099	F	H	H	CH2Ph	H	5-(2-Pyr)-2-thienyl	C ₂₉ H ₂₉ F ₂ N ₃ O ₃ S ₂
314100	Cl	H	H	i-Pr	H	5-(2-Pyr)-2-thienyl	C ₂₈ H ₂₉ Cl ₂ N ₃ O ₃ S ₂
314101	Cl	H	H	i-Pr	H	2,5-(MeO)2-Ph	C ₂₄ H ₃₂ Cl ₂ N ₂ O ₅ S
314102	F	Me	Me	H	H	5-(2-Pyr)-2-thienyl	C ₂₄ H ₂₇ F ₂ N ₃ O ₃ S ₂
314103	F	H	Me	H	H	5-(2-Pyr)-2-thienyl	C ₂₃ H ₂₅ F ₂ N ₃ O ₃ S ₂
314104	F	H	H	H	Me	5-(2-Pyr)-2-thienyl	C ₂₃ H ₂₅ F ₂ N ₃ O ₃ S ₂



314096: C23 H25 F2 N3 O3 S2

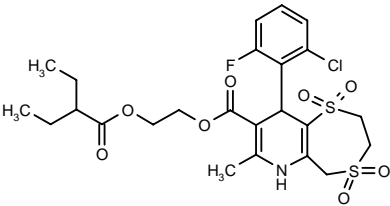
SOURCE – AstraZeneca.

REFERENCES

1. Sanganee, H. and Springthorpe, B. (AstraZeneca AB) *Chemical cpds*. WO 0192227.

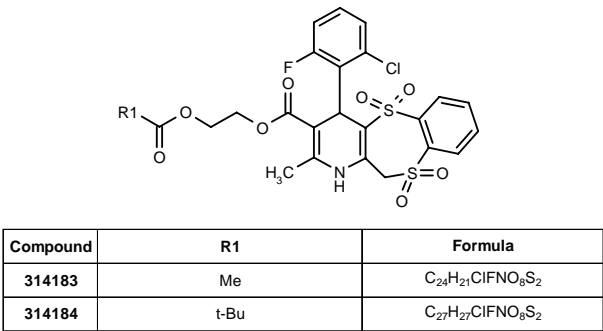
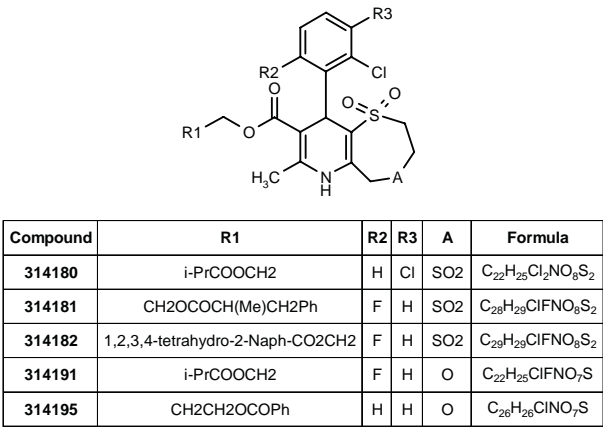
314174

9-(2-Chloro-6-fluorophenyl)-7-methyl-1,1,4,4-tetraoxo-2,3,6,9-tetrahydro-5*H*-[1,4]dithiepine[6,5-*b*]pyridine-8-carboxylic acid 2-(2-ethylbutyryloxy)ethyl ester



C24 H29 Cl F N O8 S2; Mol wt: 578.0751

ACTION – Calcium channel antagonist with an IC₅₀ value of 13 nM for inhibition of [³H]-nitrendipine binding in rabbit heart preparations. Potentially useful for the treatment of asthma, as well as hypersensitivity, allergy, bronchospasm, dysmenorrhea, esophageal spasm, glaucoma, preterm labor, urinary tract disorders, gastrointestinal motility disorders and cardiovascular disorders. Compounds of the invention are described as soft drugs, and thus are devoid of unwanted side effects. Other exemplified dihydropyridine-containing carboxylic acids are:



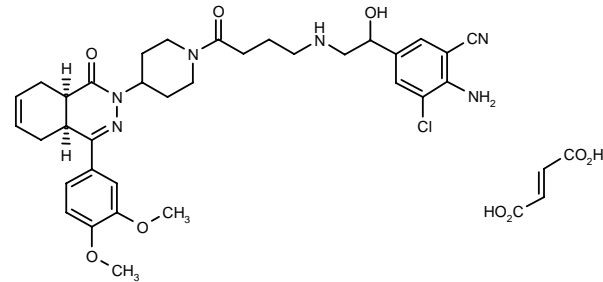
SOURCE – Ortho-McNeil.

REFERENCES

1. Dodd, J.H. et al. (Ortho-McNeil Pharmaceutical, Inc.) *Dihydropyridine soft drugs, and related compsns. and methods.* WO 0192267.

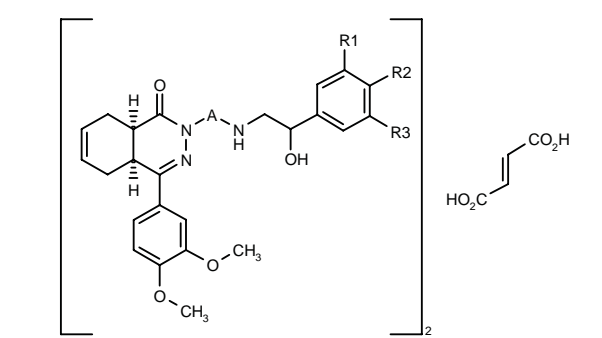
314283

2-Amino-3-chloro-5-[2-[4-[4-[(4a*S*,8a*R*)-4-(3,4-dimethoxyphenyl)-1-oxo-1,2,4a,5,8,8a-hexahydrophthalazin-2-yl]-piperidin-1-yl]-4-oxobutylamino]-1-hydroxyethyl]benzonitrile fumarate



C₃₄ H₄₁ Cl N₆ O₅ . C₄ H₄ O₄; Mol wt: 765.2595

ACTION – Dual-action compound that acts simultaneously as a β_2 -adrenoceptor agonist ($-\log EC_{50} = 8.64$) and a phosphodiesterase type 4 (PDE4) inhibitor ($-\log IC_{50} = 10.17$). Potentially useful for the treatment of airways disorders such as bronchitis, asthma and chronic obstructive pulmonary disease, as well as inflammatory and immune disorders of the skin, CNS, intestine, eyes and joints including psoriasis, eczema, skin allergies, arthritis, AIDS, multiple sclerosis, transplant rejection, septic shock, adult respiratory distress syndrome, Crohn's disease, ulcerative colitis, rhinitis, allergic conjunctivitis, cardiac insufficiency, erectile dysfunction, diabetes insipidus, Alzheimer's disease, depression and arteriosclerotic dementia. Other exemplified compounds are:



Compound	R1	R2	R3	A	Formula
314285	CN	NH2	Cl	-(CH2)4-	2C ₂₉ H ₃₄ ClN ₅ O ₄ ·C ₄ H ₄ O ₄
314287	CN	NH2	Cl	-(CH2)5-	2C ₃₀ H ₃₆ ClN ₅ O ₄ ·C ₄ H ₄ O ₄
314289	CN	NH2	Cl	-(CH2)6-	2C ₃₁ H ₃₈ ClN ₅ O ₄ ·C ₄ H ₄ O ₄
314291	CH2OH	OH	H	-(CH2)6-	2C ₃₁ H ₄₁ N ₅ O ₆ ·C ₄ H ₄ O ₄

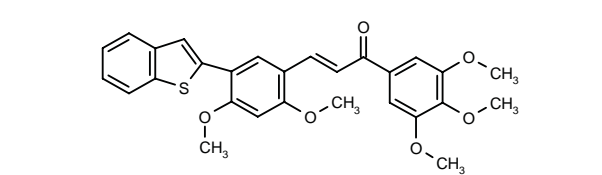
SOURCE – Byk Gulden (Altana Pharma).

REFERENCES

1. Hatzelmann, A. et al. (Byk Nederland BV) *Cpds. effective as β_2 -adrenoreceptor agonists as well as PDE4-inhibitors.* WO 0194319.

314698

3-[5-(1-Benzothien-2-yl)-2,4-dimethoxyphenyl]-1-(3,4,5-trimethoxyphenyl)-2-propen-1-one



C₂₈ H₂₆ O₆ S; Mol wt: 490.5734

ACTION – Agent with the ability to inhibit the expression of VCAM-1, found to inhibit [³H]-thymidine incorporation into serum-stimulated human aortic smooth muscle cells with an IC₅₀ of 0.33 μ M and TNF-induced VCAM-1 expression *in vitro* with an IC₅₀ of 5 μ M. In a mouse model of allergic inflammation (peritonitis), it reduced eosinophil recruit-ment in ovalbumin-sensitized mice at a dose of 50 mg/kg s.c. Compound also inhibited paw edema in methylated BSA-challenged mice at a dose of 50 mg/kg i.p. Potentially useful for the treatment of asthma, arthritis, dermatitis, psoriasis, cystic fibrosis, transplant rejection, multiple sclerosis, atherosclerosis, postangioplasty restenosis, coronary and small artery disease, angina, systemic lupus erythematosus, Crohn's disease, inflammatory bowel disease, autoimmune diabetes, diabetic retinopathy, rhinitis, ischemia–reperfusion injury, chronic obstructive pulmonary disease, glomerulone-phritis, Graves' disease, gastrointestinal allergies and conjunctivitis.

SOURCE – AtheroGenics.

REFERENCES

1. Meng, C.Q. et al. (AtheroGenics, Inc.) *1,3-Bis-(subst.d.-phenyl)-2-propen-1-ones and their use to treat VCAM-1 mediated disorders.* WO 0198291.

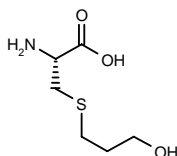
FUDOSTEINE

Prop INN

170989

S-(3-Hydroxypropyl)-L-cysteine2(*R*)-Amino-3-(3-hydroxypropylsulfanyl)propionic acidSS-320⁺

SS-320A



C6 H13 N O3 S; Mol wt: 179.2390

ACTION – Mucoactive cysteine derivative.

INDICATION – Expectorant for bronchial asthma, chronic bronchitis, bronchiectasis, pulmonary tuberculosis, pulmonary emphysema, atypical mycobacterial disease and pneumoconiosis.

PRESENTATION – Tablets, 200 mg

PROPRIETARY NAMES AND SOURCES – *Cleanal* (SSP, JP); *Spelear* (Mitsubishi Pharma, JP).

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7. Kusano, K. et al. *Effects of fudosteine, a new mucoactive drug, on the increase in mucus secretion produced by secretagogues in human pulmonary mucociliary carcinoma cells*. Pharm Sci 1997, 3403.
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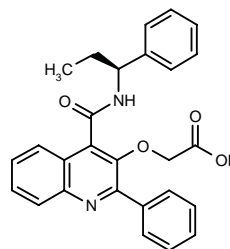
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*Drug Data Rep 1991, 013(07): 0560.

SB-235375*

253678

2-[2-Phenyl-4-[*N*-[1(*S*)-phenylpropyl]carbamoyl]quinolin-3-yloxy]acetic acid

C27 H24 N2 O4; Mol wt: 440.5030

ACTION – Potent nonpeptide tachykinin NK₃ receptor antagonist with high affinity and selectivity for the human NK₃ receptor over human NK₁ and NK₂ receptors (K_i = 2.2, > 100,000 and 209 nM, respectively); no activity was seen at other receptors, enzymes or ion channels at 1 μM. In HEK293 cells expressing the human NK₃ receptor, compound competitively antagonized NKB-induced Ca²⁺ mobilization (K_b = 12 nM); it also antagonized senktide-induced contractions in rabbit isolated iris sphincter and in guinea pig ileal circular smooth muscle (pA₂ = 8.3 and 8.1, respectively). *In vivo* it dose-dependently inhibited senktide-induced miosis in rabbits (ED₅₀ = 0.56 mg/kg i.v.), and it was also effective at doses of 10-30 mg/kg i.p. against citric acid-induced cough and airways hyperreactivity in guinea pigs. Pharmacokinetic studies in mice and rats showed good oral bioavailability and systemic absorption, but little or no CNS penetration; preliminary pharmacokinetic assessment in dogs and monkeys confirmed its good oral bioavailability (about 40%) and low to moderate clearance. Potentially useful as an antiasthmatic agent.

SOURCE – GlaxoSmithKline.

REFERENCES

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3. Giardina, G.A.M. et al. *Discovery of a novel class of selective non-peptide antagonists for the human neurokinin-3 receptor. 2. Identification of (S)-N-(1-phenylpropyl)-3-hydroxy-2-phenylquinoline-4-carboxamide (SB 223412).* J Med Chem 1999, 42(6): 1053.

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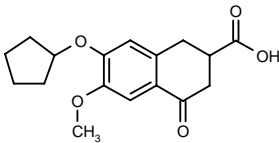
5. Ruggieri, M.R. et al. *Role of neurokinin receptors in the behavioral effect of intravesical antigen infusion in guinea pig bladder.* J Urol 2000, 164(1): 197.

*Identified compound **253678** (see **253446**) Drug Data Rep 1997, 019(10): 0893.

ST-1702

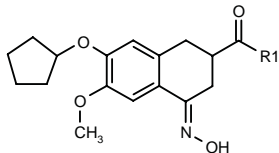
314871

7-(Cyclopentyloxy)-6-methoxy-4-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid



C17 H20 O5; Mol wt: 304.3400

ACTION – Phosphodiesterase type 4 (PDE4) inhibitor, potentially useful for the treatment of asthma and septic shock. It gave an IC₅₀ of 12.1 μM against human PDE4 and displayed no measurable affinity for the rolipram high-affinity PDE4 isoform (HPDE4), and is therefore expected to minimize side effects associated with PDE4 inhibitors such as rolipram. It was shown to be selective over other PDE subtypes, inhibiting PDE1 (bovine), PDE3 (human), PDE4 (human), PDE5 (human) and PDE6 (bovine) by 27, 22, 78, 16 and 27%, respectively, at 100 mM. Other exemplified 1,2,3,4-tetrahydronaphthalene derivatives are:



Compound	R1	Formula
ST-1703 [314872]	OH	C ₁₇ H ₂₁ NO ₅
ST-1704 [314873]	NHOH	C ₁₇ H ₂₂ N ₂ O ₅

SOURCE – Sigma-Tau.

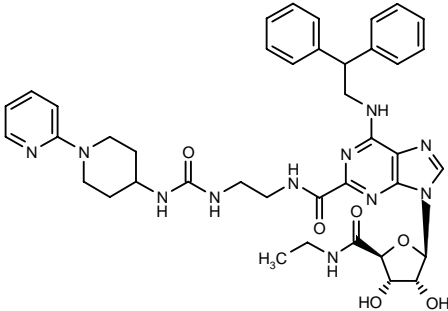
REFERENCES

1. Fanto', N. and Tinti, M.O. (Sigma-Tau Industrie Farmaceutiche Riunite SpA) *2,6,7-Substd. tetralines useful for the preparation of medicaments with phosphodiesterase IV inhibitory activity.* WO 0200609.

AGENTS FOR RESPIRATORY DISTRESS SYNDROME

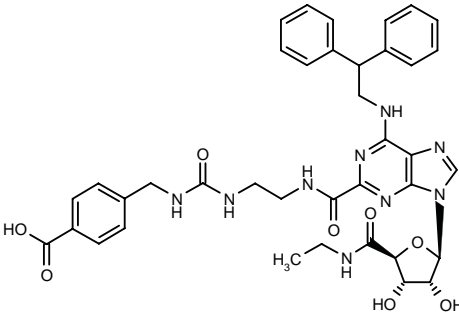
314242

1-[N⁶-(2,2-Diphenylethyl)-2-[N-[2-[3-[1-(2-pyridyl)piperidin-4-yl]ureido]ethyl]carbamoyl]adenin-9-yl]-1-deoxy-N-ethyl-β-D-ribofuranuronamide



C40 H47 N11 O6; Mol wt: 777.8823

ACTION – Selective adenosine A_{2A} receptor agonist, potentially useful for the treatment of inflammatory and respiratory disorders including adult respiratory distress syndrome, bronchitis, chronic obstructive pulmonary disease, cystic fibrosis, asthma, emphysema, bronchiectasis, chronic sinusitis, rhinitis, septic shock, male erectile dysfunction, male and female factor infertility, hypertension, stroke, epilepsy, cerebral ischemia, peripheral vascular disease, postischemic reperfusion injury, diabetes, arthritis, multiple sclerosis, psoriasis, dermatitis, ulcerative colitis, inflammatory bowel disease, gastritis and wound healing. Another related compound is:



314243: C38 H41 N9 O8

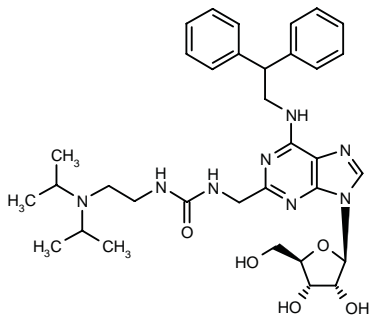
SOURCE – Pfizer.

REFERENCES

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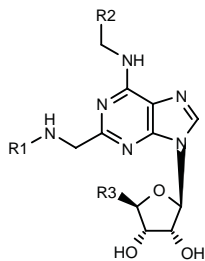
315088

2-[3-[2-(Diisopropylamino)ethyl]ureidomethyl]-N⁶-(2,2-diphenylethyl)adenosine

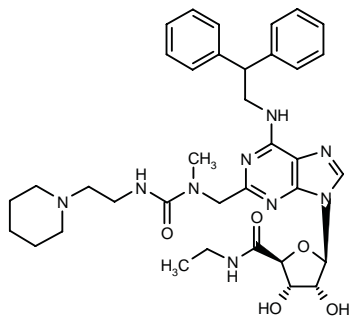


C34 H46 N8 O5; Mol wt: 646.7884

ACTION – Adenosine A_{2A} receptor agonist, potentially useful for the treatment of inflammatory respiratory diseases such as adult respiratory distress syndrome, bronchitis, chronic obstructive pulmonary disease, cystic fibrosis, asthma, emphysema, bronchiectasis, chronic sinusitis and rhinitis. Other applications include septic shock, erectile dysfunction, hypertension, stroke, epilepsy, cerebral ischemia, peripheral vascular disease, diabetes, arthritis, multiple sclerosis, psoriasis, allergic dermatitis, ulcerative colitis, Crohn’s disease, gastritis and wound healing. Other exemplified purine derivatives are:



Compound	R1	R2	R3	Formula
315089	1-Pip-CH2CH2NHC(=NCN)	CH(Ph)2	CONHEt	C ₃₆ H ₄₅ N ₁₁ O ₄
315091	2-Pyr-CH2CH2N(Me)CO	CH(Ph)2	CH2OH	C ₃₄ H ₃₈ N ₆ O ₅
315092	1,2,3,4-tetrahydro-2-iso-quinoliny-CH2CH2NHCO	CH(Ph)2	CONHEt	C ₃₉ H ₄₅ N ₉ O ₅
315095	CONHCH2CH2N(i-Pr)C(Me)2Ph	CH(Ph)2	CONHEt	C ₄₂ H ₅₃ N ₅ O ₅
315097	2,2,6,6-(Me)4-1-Pip-CH2CH2NHCO	CH(Ph)2	CH2OH	C ₃₇ H ₅₀ N ₆ O ₅
315098	CONHCH2CH2N(i-Pr)2	(4-Cl-Ph)2CH	CONHEt	C ₃₆ H ₄₇ Cl ₂ N ₉ O ₅
315099	CONHCH2CH2N(i-Pr)2	1-Naph	CONHEt	C ₃₃ H ₄₅ N ₉ O ₅



315093: C36 H47 N9 O5

SOURCE – Pfizer.

REFERENCES

1. Mantell, S.J. et al. (Pfizer Ltd.;Pfizer Inc.) *Purine derivs.* WO 0200676.

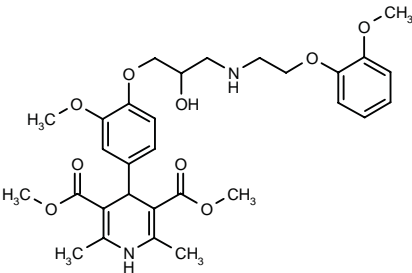
CARDIOVASCULAR DRUGS

ANTIHYPERTENSIVE DRUGS

LABEDIPINEDIOL A^{1-4,6}

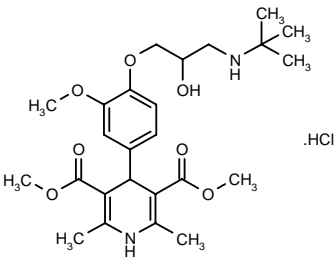
315520

4-[4-[2-Hydroxy-3-[2-(2-methoxyphenoxy)ethylamino]-propoxy]-3-methoxyphenyl]-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylic acid dimethyl ester



C30 H38 N2 O9; Mol wt: 570.6352

ACTION – Antihypertensive agent, a dihydropyridine-type calcium channel blocker (pA₂ = 8.46) with α-adrenoceptor-antagonist activity (pA₂ = 8.28). Compound also showed antagonist activity at β₁- and β₂-adrenoceptors (pA₂ = 7.43 and 6.83, respectively). In anesthetized normotensive rats, a dose of 1 mg/kg i.v. decreased blood pressure, with a maximum effect at 1 min after dosing and lasting for over 1 h. Oral administration of compound (10-50 mg/kg) to spontaneous hypertensive rats produced a potent and long-lasting antihypertensive effect. Potentially useful for the treatment of hypertension and associated cardiac hypertrophy. Another related compound is:



Vanedipinedilol [291201]:^{1,2,4,5} C25 H36 N2 O7 . HCl

SOURCE – Kaohsiung Medical College, Kaohsiung (TW).

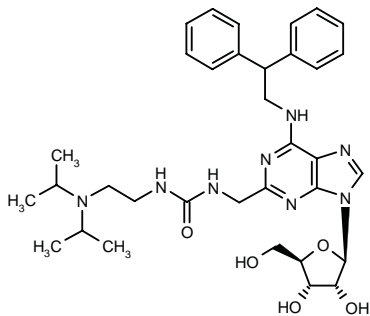
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2. Chin, E. *Dihydropyridine derivs. having guaiacoxypipranolamine and phenoxypropylamine structures.* JP 2000086633.

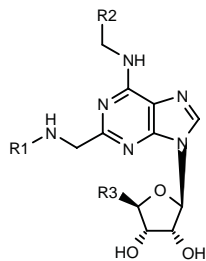
315088

2-[3-[2-(Diisopropylamino)ethyl]ureidomethyl]-N⁶-(2,2-diphenylethyl)adenosine

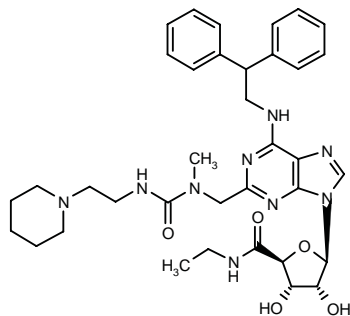


C34 H46 N8 O5; Mol wt: 646.7884

ACTION – Adenosine A_{2A} receptor agonist, potentially useful for the treatment of inflammatory respiratory diseases such as adult respiratory distress syndrome, bronchitis, chronic obstructive pulmonary disease, cystic fibrosis, asthma, emphysema, bronchiectasis, chronic sinusitis and rhinitis. Other applications include septic shock, erectile dysfunction, hypertension, stroke, epilepsy, cerebral ischemia, peripheral vascular disease, diabetes, arthritis, multiple sclerosis, psoriasis, allergic dermatitis, ulcerative colitis, Crohn’s disease, gastritis and wound healing. Other exemplified purine derivatives are:



Compound	R1	R2	R3	Formula
315089	1-Pip-CH2CH2NHC(=NCN)	CH(Ph)2	CONHEt	C ₃₆ H ₄₅ N ₁₁ O ₄
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315092	1,2,3,4-tetrahydro-2-iso-quinoliny-CH2CH2NHCO	CH(Ph)2	CONHEt	C ₃₉ H ₄₅ N ₉ O ₅
315095	CONHCH2CH2N(i-Pr)C(Me)2Ph	CH(Ph)2	CONHEt	C ₄₂ H ₅₃ N ₅ O ₅
315097	2,2,6,6-(Me)4-1-Pip-CH2CH2NHCO	CH(Ph)2	CH2OH	C ₃₇ H ₅₀ N ₆ O ₅
315098	CONHCH2CH2N(i-Pr)2	(4-Cl-Ph)2CH	CONHEt	C ₃₆ H ₄₇ Cl ₂ N ₉ O ₅
315099	CONHCH2CH2N(i-Pr)2	1-Naph	CONHEt	C ₃₃ H ₄₅ N ₉ O ₅



315093: C36 H47 N9 O5

SOURCE – Pfizer.

REFERENCES

1. Mantell, S.J. et al. (Pfizer Ltd.;Pfizer Inc.) *Purine derivs.* WO 0200676.

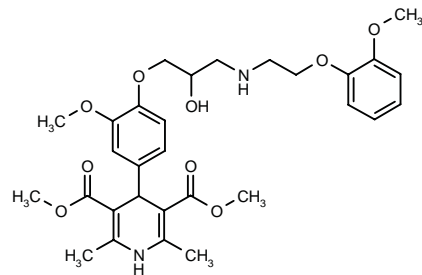
CARDIOVASCULAR DRUGS

ANTIHYPERTENSIVE DRUGS

LABEDIPINEDIOL A^{1-4,6}

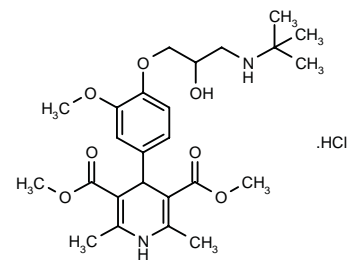
315520

4-[4-[2-Hydroxy-3-[2-(2-methoxyphenoxy)ethylamino]-propoxy]-3-methoxyphenyl]-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylic acid dimethyl ester



C30 H38 N2 O9; Mol wt: 570.6352

ACTION – Antihypertensive agent, a dihydropyridine-type calcium channel blocker (pA₂ = 8.46) with α-adrenoceptor-antagonist activity (pA₂ = 8.28). Compound also showed antagonist activity at β₁- and β₂-adrenoceptors (pA₂ = 7.43 and 6.83, respectively). In anesthetized normotensive rats, a dose of 1 mg/kg i.v. decreased blood pressure, with a maximum effect at 1 min after dosing and lasting for over 1 h. Oral administration of compound (10-50 mg/kg) to spontaneous hypertensive rats produced a potent and long-lasting antihypertensive effect. Potentially useful for the treatment of hypertension and associated cardiac hypertrophy. Another related compound is:



Vanedipinedilol [291201]:^{1,2,4,5} C25 H36 N2 O7 . HCl

SOURCE – Kaohsiung Medical College, Kaohsiung (TW).

REFERENCES

1. Chen, I.-J. and Lin, T.-H. *Guaiacoxypipranolamines with α/β-adrenergic blocking activity.* EP 1108710, WO 0005209.

2. Chin, E. *Dihydropyridine derivs. having guaiacoxypipranolamine and phenoxypropylamine structures.* JP 2000086633.

3. Liang, J.-C. et al. *Labeledipinedilol-A: A vanilloid-based α/β -adrenoceptor blocker with calcium entry blocking and long-acting antihypertensive properties.* Drug Dev Res 2000, 49(2): 94.

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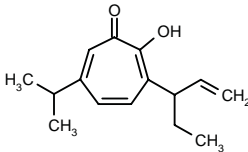
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TREATMENT OF DISORDERS OF
THE CORONARY ARTERIES
AND ATHEROSCLEROSIS

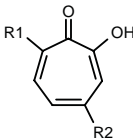
313857

3-(1-Ethyl-2-propenyl)-2-hydroxy-6-isopropyl-2,4,6-cycloheptatrien-1-one



C15 H20 O2; Mol wt: 232.3210

ACTION – An inhibitor of 12-lipoxygenase (12-LO) with respective IC₅₀ values in human platelets and porcine leukocytes of 0.01 and 0.17 μ M. Potentially useful for the treatment of cardiovascular diseases such as arteriosclerosis and ischemic cardiopathy, cerebrovascular spasm, allergic and inflammatory diseases including psoriasis and nephritis, cancer and pain. Other exemplified tropolone derivatives include the following:



Compound	R1	R2	Formula
313859	H	C5H11-ethynylene	C ₁₄ H ₁₆ O ₂
313861	H	(Z)-CH=CHC5H11	C ₁₄ H ₁₈ O ₂
313862	H	(E)-CH=CHC5H11	C ₁₄ H ₁₈ O ₂
313865	CH2N(CH2Ph)2	i-Pr	C ₂₈ H ₂₇ NO ₂

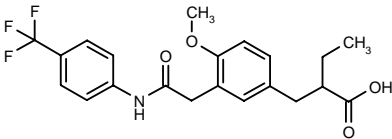
SOURCE – Nippon Shinyaku.

REFERENCES

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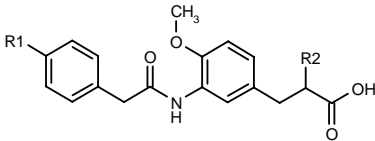
313869

2-[4-Methoxy-3-[N-[4-(trifluoromethyl)phenyl]carbamoyl-methyl]benzyl]butyric acid



C21 H22 F3 N O4; Mol wt: 409.4018

ACTION – Peroxisome proliferator-activated receptor (PPAR) agonist giving an EC₅₀ of 0.015 μ M at PPAR α receptors expressed in CHO cells. Potentially useful for the treatment of arteriosclerosis. Other exemplified 3-phenylpropionic acid derivatives are:



Compound	R1	R2	Formula
313871	Ph	H	C ₂₄ H ₂₃ NO ₄
313872	OCH2Ph	Et	C ₂₇ H ₂₉ NO ₅
313873	OPh	OMe	C ₂₆ H ₂₅ NO ₆

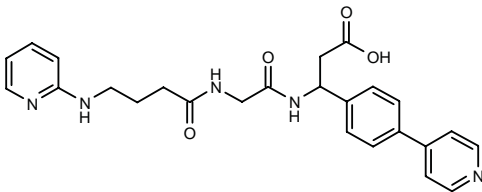
SOURCE – Kyorin.

REFERENCES

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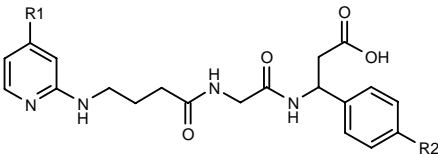
314484

3-[2-[4-(Pyridin-2-ylamino)butyramido]acetamido]-3-[4-(4-pyridyl)phenyl]propionic acid



C25 H27 N5 O4; Mol wt: 461.5193

ACTION – An inhibitor of integrin receptors, particularly $\alpha_v\beta_3$ (vitronectin), $\alpha_v\beta_5$ and $\alpha_{IIb}\beta_3$ receptors, potentially useful for the treatment of thrombosis, myocardial infarction, coronary diseases, arteriosclerosis, cancer, osteoporosis, inflammation, infections and postangioplasty restenosis. Other specifically claimed pyridyl-containing glycyL- β -alanine derivatives are:



Compound	R1	R2	Formula
314486	Me	4-Pyr	C ₂₆ H ₂₉ N ₅ O ₄
314487	H	3-Pyr	C ₂₆ H ₂₇ N ₅ O ₄
314488	Me	8-quinolyl	C ₃₀ H ₃₁ N ₅ O ₄
314489	H	8-quinolyl	C ₂₉ H ₂₉ N ₅ O ₄
314490	H	7-indolyl	C ₂₈ H ₂₉ N ₅ O ₄
314491	Me	3-thienyl	C ₂₅ H ₂₈ N ₄ O ₄ S
314492	H	3-thienyl	C ₂₄ H ₂₆ N ₄ O ₄ S

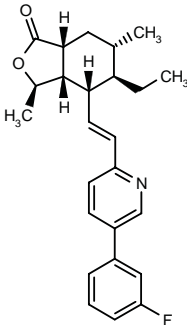
SOURCE – Merck KGaA.

REFERENCES

1. Hölzemann, G. and Goodman, S. (Merck Patent GmbH) *Pyridine-2-yl-aminoalkylcarbonylglycyl-beta-alanine and derivs. thereof.* DE 10028402, WO 0196365.

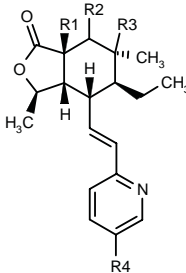
314528

(3*R*,3*aS*,4*S*,5*R*,6*S*,7*aR*)-5-Ethyl-4-[2-[5-(3-fluorophenyl)-pyridin-2-yl]vinyl]-3,6-dimethylperhydroisobenzofuran-1-one



C₂₅ H₂₈ F N O₂; Mol wt: 393.4992

ACTION – Antagonist of thrombin and/or cannabinoid CB₂ receptors, potentially useful for the treatment of atherosclerosis, restenosis, hypertension, angina pectoris, arrhythmia, heart failure, myocardial infarction, glomerulonephritis, thrombotic and thromboembolic stroke, peripheral vascular diseases, cerebral ischemia, rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, diabetes, osteoporosis, renal ischemia, nephritis, inflammatory disorders of the lung and gastrointestinal tract, reversible airways obstruction, chronic asthma and bronchitis. Other exemplified compounds include the following:



Compound	R1	R2	R3	R4	Formula
314529	H	H	H	3-CF ₃ -Ph	C ₂₆ H ₂₈ F ₃ N ₂ O ₂
314530	H	H	H	3-Cl-Ph	C ₂₆ H ₂₈ ClNO ₂
314531	OH	H	H	3-F-Ph	C ₂₅ H ₂₈ FNO ₃
314532	OH	H	H	Ph	C ₂₅ H ₂₉ NO ₃
314533	H	bond		3-F-Ph	C ₂₅ H ₂₆ FNO ₂
314534	H	H	H	2-oxazolyl	C ₂₂ H ₂₆ N ₂ O ₃
314536	OH	H	H	1-imidazolyl	C ₂₂ H ₂₇ N ₃ O ₃
314538	OH	H	H	5-tetrazolyl	C ₂₀ H ₂₅ N ₅ O ₃

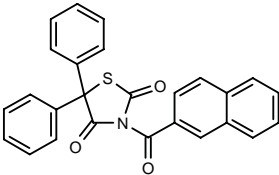
SOURCE – Schering-Plough.

REFERENCES

1. Chackalamannil, S. et al. (Schering Corp.) *Thrombin receptor antagonists.* WO 0196330.

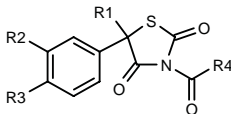
314545

3-(Naphthalen-2-ylcarbonyl)-5,5-diphenylthiazolidine-2,4-dione



C₂₆ H₁₇ N O₃ S; Mol wt: 423.4903

ACTION – Chymase inhibitor (IC₅₀ = 9.9 nM), potentially useful for the treatment of cardiovascular diseases such as postangioplasty restenosis, hypertension, arteriosclerosis, myocardial infarction, cardiac hypertrophy, heart failure, diabetic and nondiabetic nephropathy and peripheral vascular disorders, ophthalmic circulatory disorders, inflammation and allergic diseases, as well as for modulating ciliary muscle contraction and relaxation. Other exemplified thiazolidine-2,4-dione derivatives are:



Compound	R1	R2	R3	R4	Formula
314546	H	EtO	C ₅ H ₁₁ O	2-Naph	C ₂₇ H ₂₇ NO ₃ S
314547	H	EtO	C ₅ H ₁₁ O	1-Naph	C ₂₇ H ₂₇ NO ₃ S
314548	Ph	H	H	1-Naph	C ₂₆ H ₁₇ N ₃ O ₃ S

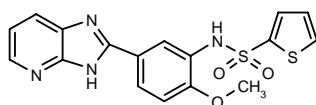
SOURCE – Senju.

REFERENCES

1. Sakai, Y. and Inoue, J. (Senju Pharmaceuticals Co., Ltd.) *Novel thiazolidinedione derivs. and use thereof as drugs.* WO 0194326.

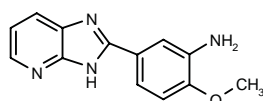
314549

N-[5-(3*H*-Imidazo[4,5-*b*]pyridin-2-yl)-2-methoxyphenyl]-thiophene-2-sulfonamide



C17 H14 N4 O3 S2; Mol wt: 386.4546

ACTION – An inhibitor of 15-lipoxygenase (IC_{50} = 10 μ M) with potential utility in the treatment of atherosclerosis and inflammatory disorders such as asthma and arthritis. Another exemplified 6,5-fused bicyclic heterocycle is:



314550: C13 H12 N4 O

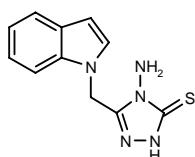
SOURCE – Pfizer.

REFERENCES

1. Picard, J.A. et al. (Pfizer Inc.) *6,5-Fused bicyclic heterocycles*. WO 0196336.

315635

4-Amino-5-(1*H*-indol-1-ylmethyl)-3,4-dihydro-2*H*-1,2,4-triazole-3-thione



C11 H11 N5 S; Mol wt: 245.3089

ACTION – Antioxidant proven to strongly inhibit lipid peroxidation in rat liver microsomes by 96% at 50 μ M. *In vivo*, a dose of 100 μ mol/kg i.v. protected against oxidative damage induced in rabbit heart by ischemia–reperfusion injury; no effects on hemodynamic parameters were seen. Potentially useful for the treatment of myocardial infarction.

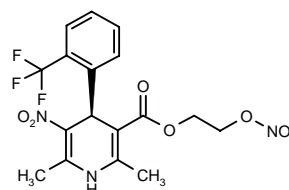
SOURCES – Aristotle University of Thessaloniki, Thessaloniki (GR); University of Athens, Athens (GR); Onassis Cardiac Surgery Center, Athens (GR).

REFERENCES

1. Andreadou, I. et al. *Antioxidant activity of novel indole derivatives and protection of the myocardial damage in rabbits*. Chem Pharm Bull 2002, 50(2): 165.

HEART FAILURE THERAPY**285329**

(–)-2,6-Dimethyl-5-nitro-4(*S*)-[2-(trifluoromethyl)phenyl]-1,4-dihydropyridine-3-carboxylic acid 2-(nitrooxy)ethyl ester



C17 H16 F3 N3 O7; Mol wt: 431.3214

ACTION – Calcium channel modulator with cardio-selective agonist activity in guinea pig left atrium (EC_{50} = 0.92 μ M) and selective smooth muscle antagonist activity in guinea pig ileum (IC_{50} = 16 μ M). In whole-cell voltage-clamp studies in isolated guinea pig ventricular myocytes, compound exerted weak antagonism on L-type voltage-sensitive calcium current at the concentration of 10 μ M. Potentially useful for the treatment of heart failure.

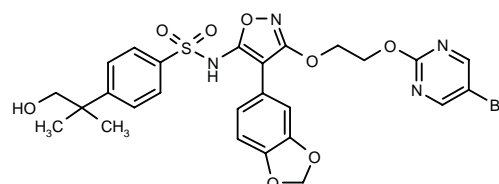
SOURCES – University of Alberta, Edmonton, AB (CA); Dalhousie University, Halifax, NS (CA).

REFERENCES

1. Shan, R. and Knaus, E.E. *The design of (–)-(S)-nitrooxyethyl 1,4-dihydro-2,6-dimethyl-3-nitro-4-(2-trifluoromethylphenyl)pyridine-5-carboxylate: A cardioselective positive inotropic derivative of Bay K 8644*. Bioorg Med Chem Lett 1999, 9(17): 2613.
2. Shan, R. et al. *Syntheses, calcium channel agonist-antagonist modulation activities, nitric oxide release, and voltage-clamp studies of 2-nitrooxyethyl 1,4-dihydro-2,6-dimethyl-3-nitro-4-(2-trifluoromethylphenyl)pyridine-5-carboxylate enantiomers*. J Med Chem 2002, 45(4): 955.

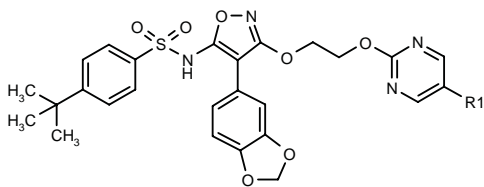
313538

N-[4-(1,3-Benzodioxol-5-yl)-3-[2-(5-bromopyrimidin-2-yloxy)ethoxy]isoxazol-5-yl]-4-(2-hydroxy-1,1-dimethylethyl)benzenesulfonamide



C26 H25 Br N4 O8 S; Mol wt: 633.4735

ACTION – Endothelin (ET) receptor antagonist with selectivity for ET_A over ET_B receptor subtypes. Potentially useful for the treatment of congestive heart failure, acute and chronic renal failure, restenosis and pulmonary hypertension, among other endothelin-mediated conditions. Other exemplified *N*-(5-isoxazolyl)sulfonamide derivatives are:



Compound	R1	Formula
313540	Br	C ₂₆ H ₂₅ BrN ₄ O ₇ S
313541	Cl	C ₂₆ H ₂₅ ClN ₄ O ₇ S
313543	SMe	C ₂₇ H ₂₈ N ₄ O ₇ S ₂
313545	SO ₂ Me	C ₂₇ H ₂₈ N ₄ O ₈ S ₂

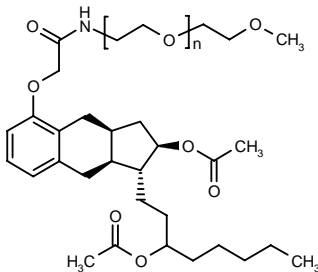
SOURCE – Pfizer.

REFERENCES

1. Baks, B.J. et al. (Pfizer Ltd.;Pfizer Inc.) *N*-(Isoxazol-5-yl)-sulfonamide derivs. and their use as endothelin antagonists. EP 1160248.

314417

Acetic acid 1-[2-[(1*R*,2*R*,3*aS*,9*aS*)-2-acetoxy-5-[*N*-(ω-methoxy polyethylene glycol)carbamoylmethoxy]-2,3,3*a*,4,9,9*a*-hexahydro-1*H*-cyclopenta[*b*]naphthalen-1-yl]ethyl]hexyl ester



ACTION – A representative compound from a series of prostaglandin analogues claimed for use in the treatment of congestive heart failure. This compound was shown to decrease mean arterial pressure in anesthetized rats, without affecting heart rate, following either oral or i.v. administration.

SOURCE – United Therapeutics.

REFERENCES

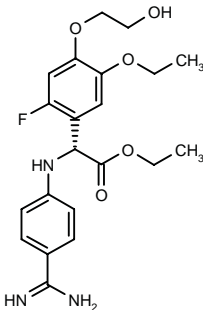
1. Shorr, R. et al. (United Therapeutics Corp.) *Prostaglandin cpds. for treating congestive heart failure*. WO 0193862.

AGENTS AFFECTING BLOOD COAGULATION

ANTICOAGULANTS

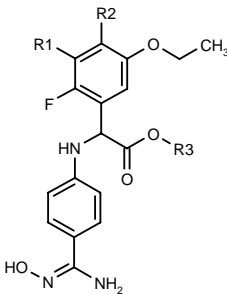
313722

2(*R*)-(4-Amidinophenylamino)-2-[5-ethoxy-2-fluoro-4-(2-hydroxyethoxy)phenyl]acetic acid ethyl ester



C21 H26 F N3 O5; Mol wt: 419.4504

ACTION – Anticoagulant with the ability to inhibit the formation of the coagulation factors Xa, IXa and thrombin induced by factor VIIa and tissue factor. Potentially useful for the treatment of thrombosis, stroke, myocardial infarction, inflammation, arteriosclerosis and cancer. Other specifically claimed phenylglycine derivatives are:

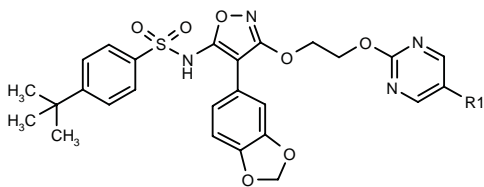


Compound	R1	R2	R3	Isomer	Formula
313723	H	OCH ₂ CH ₂ OH	H	R	C ₁₉ H ₂₂ FN ₃ O ₆
313724	3(S)-THF-O	H	Et		C ₂₃ H ₂₈ FN ₃ O ₆

SOURCE – Roche.

REFERENCES

1. Alig, L. et al. (F. Hoffmann-La Roche AG) *Phenylglycine derivs*. WO 0190051.



Compound	R1	Formula
313540	Br	C ₂₆ H ₂₅ BrN ₄ O ₇ S
313541	Cl	C ₂₆ H ₂₅ ClN ₄ O ₇ S
313543	SMe	C ₂₇ H ₂₈ N ₄ O ₇ S ₂
313545	SO ₂ Me	C ₂₇ H ₂₈ N ₄ O ₈ S ₂

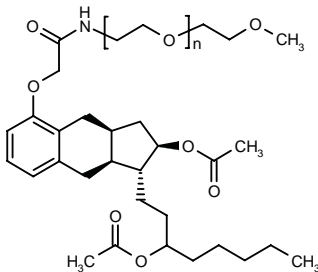
SOURCE – Pfizer.

REFERENCES

1. Baks, B.J. et al. (Pfizer Ltd.;Pfizer Inc.) *N*-(Isoxazol-5-yl)-sulfonamide derivs. and their use as endothelin antagonists. EP 1160248.

314417

Acetic acid 1-[2-[(1*R*,2*R*,3*aS*,9*aS*)-2-acetoxy-5-[*N*-(ω-methoxy polyethylene glycol)carbamoylmethoxy]-2,3,3*a*,4,9,9*a*-hexahydro-1*H*-cyclopenta[*b*]naphthalen-1-yl]ethyl]hexyl ester



ACTION – A representative compound from a series of prostaglandin analogues claimed for use in the treatment of congestive heart failure. This compound was shown to decrease mean arterial pressure in anesthetized rats, without affecting heart rate, following either oral or i.v. administration.

SOURCE – United Therapeutics.

REFERENCES

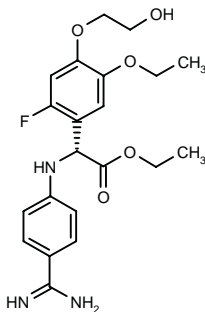
1. Shorr, R. et al. (United Therapeutics Corp.) *Prostaglandin cpds. for treating congestive heart failure*. WO 0193862.

AGENTS AFFECTING BLOOD COAGULATION

ANTICOAGULANTS

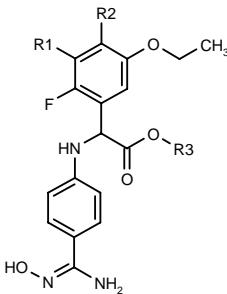
313722

2(*R*)-(4-Amidinophenylamino)-2-[5-ethoxy-2-fluoro-4-(2-hydroxyethoxy)phenyl]acetic acid ethyl ester



C21 H26 F N3 O5; Mol wt: 419.4504

ACTION – Anticoagulant with the ability to inhibit the formation of the coagulation factors Xa, IXa and thrombin induced by factor VIIa and tissue factor. Potentially useful for the treatment of thrombosis, stroke, myocardial infarction, inflammation, arteriosclerosis and cancer. Other specifically claimed phenylglycine derivatives are:



Compound	R1	R2	R3	Isomer	Formula
313723	H	OCH ₂ CH ₂ OH	H	R	C ₁₉ H ₂₂ FN ₃ O ₆
313724	3(S)-THF-O	H	Et		C ₂₃ H ₂₈ FN ₃ O ₆

SOURCE – Roche.

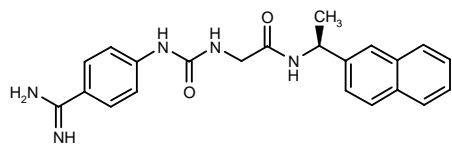
REFERENCES

1. Alig, L. et al. (F. Hoffmann-La Roche AG) *Phenylglycine derivs*. WO 0190051.

313891

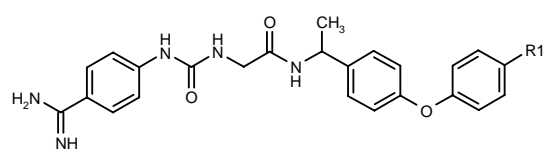
2-[3-(4-Amidinophenyl)ureido]-N-[1(S)-(2-naphthyl)ethyl]-acetamide

1-(4-Amidinophenyl)-3-[N-[1(S)-(2-naphthyl)ethyl]-carbamoylmethyl]urea



C22 H23 N5 O2; Mol wt: 389.4567

ACTION – Anticoagulant, an inhibitor of factor VIIa (K_i = 0.026 μ M), potentially useful for preventing blood clotting or an inflammatory response in the treatment of cardiovascular disorders, thromboembolic diseases and restenosis. Other exemplified compounds within this series of urea and thiourea derivatives are:



Compound	R1	Formula
313892	OMe	C ₂₈ H ₂₇ N ₅ O ₄
313893	NO2	C ₂₄ H ₂₄ N ₆ O ₅

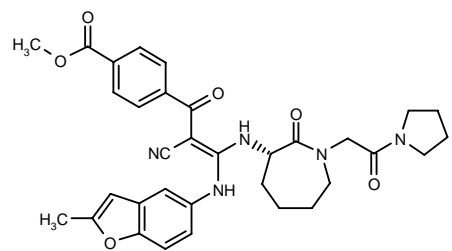
SOURCE – Aventis Pharma.

REFERENCES

1. Klingler, O. et al. (Aventis Pharma Deutschland GmbH) *Factor VIIa inhibitory (thio)urea derivs., their preparation and their use.* EP 1162194, WO 0194301.

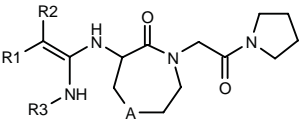
314556

4-[2-Cyano-3-(2-methyl-1-benzofuran-5-ylamino)-3-[2-oxo-1-[2-oxo-2-(1-pyrrolidinyl)ethyl]perhydroazepin-3(S)-ylamino]-2-propenoyl]benzoic acid methyl ester



C33 H35 N5 O6; Mol wt: 597.6685

ACTION – Anticoagulant, an inhibitor of factor Xa with potential in the treatment of thrombotic disorders such as myocardial infarction, unstable angina, thromboembolic stroke, venous thrombosis, pulmonary embolism, peripheral occlusive arterial disease, postsurgical thromboembolic complications, atherosclerosis, coagulopathy, disseminated intravascular coagulation, etc. Other exemplified compounds are:



Compound	R1	R2	R3	A	Isomer	Formula
314557	CN	CN	2-Me-5-benzofuryl	-(CH2)2-		C ₂₆ H ₃₀ N ₆ O ₃
314558	H	NO2	2-Me-5-benzothiazolyl	-CH2-	S	C ₂₂ H ₂₈ N ₆ O ₄ S
314559	CN	CN	4-MeO-3-Me-Ph	-CH2-	S	C ₂₄ H ₃₀ N ₆ O ₃
314560	CN	CO2Me	3-NH2-1,2-benzisoxazol-5-yl	-CH2-	S	C ₂₄ H ₂₉ N ₇ O ₅
314561	CN	SO2Me	2-Me-5-benzofuryl	-CH2-	S	C ₂₅ H ₃₁ N ₅ O ₅ S
314562	CN	2-thienyl-SO2	2-Me-5-benzofuryl	-CH2-	S	C ₂₈ H ₃₁ N ₅ O ₅ S ₂
314563	CN	CO2Me	3-Cl-7-indolyl	-CH2-	S	C ₂₅ H ₂₉ ClN ₆ O ₄
314564	CN	CN	7-indolyl	-CH2-	S	C ₂₄ H ₂₇ N ₇ O ₂

SOURCE – Bristol-Myers Squibb.

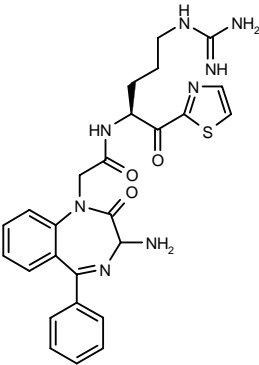
REFERENCES

1. Stein, P.D. et al. (Bristol-Myers Squibb Co.) *Lactam inhibitors of factor Xa and method.* WO 0196331.

314585

2-(3-Amino-2-oxo-5-phenyl-2,3-dihydro-1H-1,4-benzodiazepin-1-yl)-N-[4-guanidino-1(S)-(thiazol-2-ylcarbonyl)-butyl]acetamide

2-[N²-[2-(3-Amino-2-oxo-5-phenyl-2,3-dihydro-1H-1,4-benzodiazepin-1-yl)acetyl]-L-arginyl]thiazole



C26 H28 N8 O3 S; Mol wt: 532.6262

ACTION – A representative compound from a series of 2,3-dihydro-1H-1,4-benzodiazepin-2-one derivatives that act as inhibitors of factor Xa. Potentially useful for the treatment of thrombotic disorders including unstable angina, refractory angina, myocardial infarction, transient ischemic attacks, thrombotic stroke, embolic stroke, disseminated intravascular coagulation, deep venous thrombosis, pulmonary embolism and reocclusion or restenosis of reperfused coronary arteries.

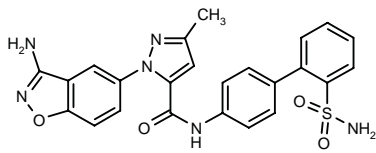
SOURCE – Millennium.

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1. Scarborough, R. (COR Therapeutics, Inc.) *Selective factor Xa inhibitors.* US 6333321.

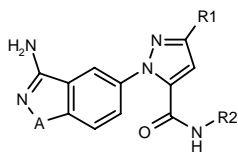
314952

1-(3-Amino-1,2-benzisoxazol-5-yl)-3-methyl-N-(2'-sulfamoylbiphenyl-4-yl)-1H-pyrazole-5-carboxamide



C24 H20 N6 O4 S; Mol wt: 488.5260

ACTION – Factor Xa inhibitor for use in the prevention and treatment of thromboembolic disorders including unstable angina, myocardial infarction, ischemic sudden death, transient ischemic attack, stroke, atherosclerosis, venous thrombosis, thrombophlebitis, arterial embolism, coronary and cerebral arterial thrombosis, and cerebral, kidney and pulmonary embolism. Other exemplified compounds include the following:



Compound	R1	R2	A	Formula
314955	Me	7-isoquinolinyl	O	C ₂₁ H ₁₆ N ₆ O ₂
314956	CF3	2-F-4-(2-Et-1-imidazolyl)-Ph	O	C ₂₃ H ₁₇ F ₄ N ₇ O ₂
314957	Et	4-(2-Me-1-imidazolyl)-Ph	O	C ₂₃ H ₂₁ N ₇ O ₂
314959	CF3	4-(2-NH2-1-imidazolyl)-Ph	O	C ₂₁ H ₁₅ F ₃ N ₆ O ₂
314961	CF3	2-F-4-(1-pyrrolidinyl-CO)-Ph	NH	C ₂₃ H ₁₉ F ₄ N ₇ O ₂
314962	CF3	2-F-4-[2-(1-Piz-CH2)-Ph]-Ph	O	C ₂₉ H ₂₅ F ₄ N ₇ O ₂
314963	Et	2-F-4-[2-[N(Me)2CH2]-1-imidazolyl]-Ph	O	C ₂₆ H ₂₅ FN ₈ O ₂

SOURCE – Bristol-Myers Squibb.

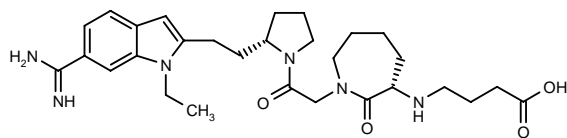
REFERENCES

1. Lam, P.Y. et al. (DuPont Pharmaceuticals Co.) *Guanidine mimics as factor Xa inhibitors*. US 6339099.

AT-1459

316718

4-[1-[2-[2(S)-[2-(6-Amidino-1-ethyl-1H-indol-2-yl)ethyl]pyrrolidin-1-yl]-2-oxoethyl]-2-oxohexahydro-1H-azepin-3(S)-ylamino]butyric acid



C29 H42 N6 O4; Mol wt: 538.6888

ACTION – Orally available antithrombotic agent, a potent and competitive thrombin inhibitor ($K_i = 49 \text{ nM}$) with high selectivity over other serine proteases including factor Xa, factor XIa, plasmin, kallikrein and activated protein C ($K_i > 219 \text{ nM}$). In rats, compound strongly inhibited thrombus formation at low i.v. doses ($ED_{50} = 0.04 \text{ mg/kg}$ i.v. bolus + 0.04 mg/kg/h by i.v. infusion) and prolonged bleeding time by 2-fold at the dose of 0.9 mg/kg by i.v. bolus + 0.9 mg/kg/h by i.v. infusion. In a rat model of carotid artery thrombosis produced by topical application of $FeCl_2$, compound significantly improved vessel patency at a dose of 0.6 mg/kg by i.v. bolus + 0.6 mg/kg/h by i.v. infusion, as well as at the oral dose of 30 mg/kg .

SOURCES – C & C Research; Chugai.

REFERENCES

1. Koo, B.-A. et al. (C & C Research Laboratories) *Subst. aromatic amidine deriv. and medicinal compsn. comprising the same*. WO 0055156.

2. Cho, J.H. et al. *The antithrombotic efficacy of AT-1459 a novel, direct thrombin inhibitor, in rat models of venous and arterial thrombosis*. Thromb Haemost 2001, 86(6): 1512.

ANTIPLATELET THERAPY

FAB-6B4

316436

Humanized anti-platelet glycoprotein Ib (gplb) murine monoclonal antibody Fab fragment

ACTION – Antithrombotic agent, a Fab fragment of a platelet glycoprotein gplb monoclonal antibody, proven to inhibit platelet aggregation induced by ristocetin ($IC_{50} = 1.2$ and $3.2 \text{ }\mu\text{g/ml}$ in human and baboon platelets, respectively) and botrocetin ($IC_{50} = 2.1 \text{ }\mu\text{g/ml}$ in human platelets). In a baboon model of arterial thrombosis, bolus doses of $80\text{-}160 \text{ }\mu\text{g/kg}$ significantly reduced platelet deposition onto a collagen surface by 43-65%; only the higher dose produced a significant prolongation of bleeding time. In a baboon model of femoral artery stenosis, a bolus dose of 2 mg/kg completely reduced the cyclic flow reductions without prolonging bleeding time. A strong antithrombotic effect was achieved in combination with a gplIb/IIIa blocker.

SOURCES – Katholieke Universiteit Leuven, Leuven (BE); ThromboGenics.

REFERENCES

1. Deckmyn, H. and Cauwenberghs, N. (Katholieke Universiteit Leuven) *Cell lines, ligands and antibody fragments for use in pharmaceutical compsns. for preventing and treating haemostasis disorders*. WO 0110911.

2. Cauwenberghs, N. et al. *Antithrombotic effect of platelet glycoprotein Ib-blocking monoclonal antibody Fab fragments in nonhuman primates*. Arterioscler Thromb Vasc Biol 2000, 20(5): 1347.

3. Wu, D. et al. *Inhibition of platelet glycoprotein Ib, glycoprotein IIb/IIIa, or both by monoclonal antibodies prevents arterial thrombosis in baboons*. Arterioscler Thromb Vasc Biol 2002, 22(2): 323.

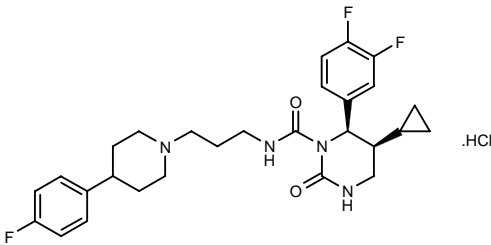
4. *Product portfolio*. ThromboGenics Web Site 2002, March 4.

RENAL–UROLOGIC DRUGS

BENIGN PROSTATIC HYPERPLASIA
THERAPY

313549

cis-5-Cyclopropyl-6-(3,4-difluorophenyl)-*N*-[3-[4-(4-fluorophenyl)piperidin-1-yl]propyl]-2-oxoperhydropyrimidine-1-carboxamide hydrochloride isomer A



C28 H33 F3 N4 O2 . HCl; Mol wt: 551.0496

ACTION – α_{1A} -Adrenoceptor antagonist with selectivity over α_{1B} - and α_{1D} -adrenoceptor subtypes and the ability to relax lower urinary tract tissue. Potentially useful for the treatment of benign prostatic hyperplasia.

SOURCE – Merck & Co.

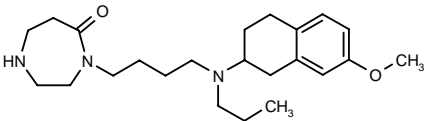
REFERENCES

1. Evans, B.E. and Gilbert, K.F. (Merck & Co., Inc.) *Lactam and cyclic urea derivs. useful as α 1a adrenoceptor antagonists.* US 6326372.

TREATMENT OF URINARY
INCONTINENCE

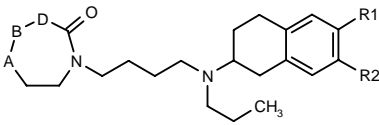
313646

4-[4-[*N*-(7-Methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)-*N*-propylamino]butyl]perhydro-1,4-diazepin-5-one



C23 H37 N3 O2; Mol wt: 387.5643

ACTION – Selective muscarinic M_2/M_3 receptor antagonist with potential in the treatment of diseases associated with smooth muscle dysfunction including diseases of the genitourinary tract such as urinary incontinence, diseases of the gastrointestinal tract including irritable bowel syndrome, as well as respiratory tract disorders. Other specifically claimed aminoalkyl-substituted lactams include the following:



Compound	R1	R2	A	B	D	Formula
313649	H	OMe	CH2	NH	CH2	C ₂₃ H ₃₇ N ₃ O ₂
313650	H	3,5-(Me)2-5-isoxazoly-SO2O	NH	CH2	CH2	C ₂₇ H ₄₀ N ₄ O ₅ S
313651	Br	H	CH2	CH2	O	C ₂₂ H ₃₃ BrN ₂ O ₂

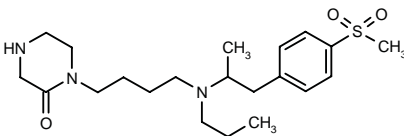
SOURCE – Roche.

REFERENCES

1. Madera, A.M. et al. (F. Hoffmann-La Roche AG) *Substd. 1-aminoalkyl-lactams and their use as muscarinic receptor antagonists.* WO 0190082.

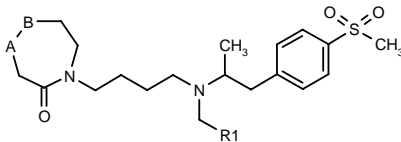
313652

1-[4-[*N*-[1-Methyl-2-[4-(methylsulfonyl)phenyl]ethyl]-*N*-propylamino]butyl]piperazin-2-one



C21 H35 N3 O3 S; Mol wt: 409.5915

ACTION – Selective muscarinic M_2/M_3 receptor antagonist with potential in the treatment of diseases associated with smooth muscle dysfunction including diseases of the genitourinary tract such as urinary incontinence, diseases of the gastrointestinal tract including irritable bowel syndrome, as well as respiratory tract disorders. Other specifically claimed aminoalkyl-substituted lactams include the following:



Compound	R1	A	B	Isomer	Formula
313653	Me	CH2	CH2		C ₂₂ H ₃₆ N ₂ O ₃ S
313655	Et	NH	CH2	S	C ₂₂ H ₃₇ N ₃ O ₃ S
313656	vinyl	CH2	NH		C ₂₂ H ₃₈ N ₃ O ₃ S

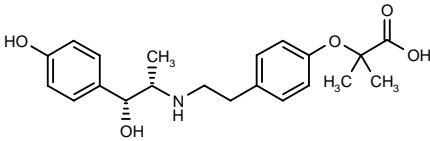
SOURCE – Roche.

REFERENCES

1. Dvorak, C.A. et al. (F. Hoffmann-La Roche AG) *Substd. 1-aminoalkyl-lactams and their use as muscarinic receptor antagonists.* WO 0190081.

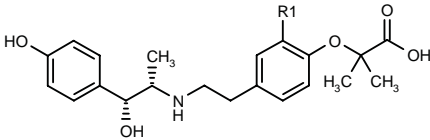
314841

2-[4-[2-[2-(*R*)-2-Hydroxy-2-(4-hydroxyphenyl)-1-(*S*)-methylethylamino]ethyl]phenoxy]-2-methylpropionic acid



C21 H27 N O5; Mol wt: 373.4463

ACTION – Potent β_3 -adrenoceptor agonist (pEC_{50} = 8.11 for relaxation of ferret detrusor) with high selectivity relative to β_1 -adrenoceptors (pEC_{20} = 4.64 for increasing heart rate in isolated rat atrium) and β_2 -adrenoceptors (pIC_{50} = 5.14 for inhibition of spontaneous motility in rat uterus). In anesthetized rats, compound lowered the intrabladder pressure with an ED_{50} value of 31 μ g/kg i.v., without increasing heart rate; for comparison, isoproterenol showed 50-fold higher potency (ED_{50} = 0.6 μ g/kg i.v.) but strongly increased heart rate. Potentially useful for the treatment of urinary incontinence. Other related compounds are:



Compound	R1	Formula
314313	Cl	C ₂₁ H ₂₆ ClNO ₅
314314	Me	C ₂₂ H ₂₉ NO ₅

SOURCE – Kissei.

REFERENCES

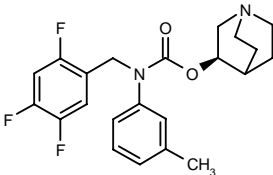
1. Tamai, T. et al. (Kissei Pharmaceutical Co., Ltd.) *2-Methylpropionic acid derivs. and medicinal compns. containing the same*. EP 1072583, WO 9952856.

2. Tanaka, N. et al. β_3 - Adrenoceptor agonists for the treatment of frequent urination and urinary incontinence: 2-[4-(2-[[1*S*,2*R*)-2-Hydroxy-2-(4-hydroxyphenyl)-1-methyl-ethyl]ethyl) phenoxy]-2-methylpropionic acid. *Bioorg Med Chem* 2001, 9(12): 3265.

314874

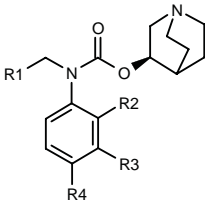
N-(3-Methylphenyl)-*N*-(2,4,5-trifluorobenzyl)carbamic acid 1-azabicyclo[2.2.2]oct-3(*R*)-yl ester

N-(3-Methylphenyl)-*N*-(2,4,5-trifluorobenzyl)carbamic acid quinuclidin-3(*R*)-yl ester



C22 H23 F3 N2 O2; Mol wt: 404.4297

ACTION – A selective muscarinic M_3 receptor antagonist proven to display a K_i of 0.031 nM against M_3 receptors and to exhibit > 800-fold selectivity over the M_2 receptor subtype. Potentially useful for the treatment of urinary incontinence, irritable bowel syndrome, respiratory diseases such as chronic obstructive pulmonary disease, chronic bronchitis, asthma, pulmonary emphysema and rhinitis, as well as in ophthalmic interventions. Other exemplified carbamic acid quinuclidin-3-yl esters are:



Compound	R1	R2	R3	R4	Formula
314875	3-F-Ph	H	F	H	C ₂₁ H ₂₂ F ₂ N ₂ O ₂
314876	2,3-(F)2-Ph	H	Cl	H	C ₂₁ H ₂₁ ClF ₂ N ₂ O ₂
314877	2-F-4-MeO-Ph	H	Cl	H	C ₂₂ H ₂₄ ClFN ₂ O ₃
314878	2,3,4-(F)3-Ph	H	Cl	H	C ₂₁ H ₂₀ ClF ₃ N ₂ O ₂
314879	3,4,5-(F)3-Ph	H	F	H	C ₂₁ H ₂₀ F ₄ N ₂ O ₂
314880	3,4,5-(F)3-Ph	H	H	F	C ₂₁ H ₂₀ F ₄ N ₂ O ₂
314881	4-t-Bu-Ph	H	H	H	C ₂₈ H ₃₂ N ₂ O ₂
314882	cyclobutyl	H	H	H	C ₁₉ H ₂₆ N ₂ O ₂
314883	cyclohexyl	F	H	H	C ₂₁ H ₂₉ FN ₂ O ₂

SOURCE – Salvat.

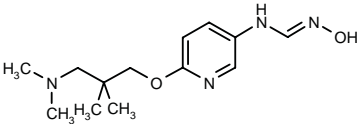
REFERENCES

1. Farrerons Gallemi, C. et al. (Laboratorios Salvat SA) *Carbamates derived from arylalkylamines*. WO 0200652.

TREATMENT OF RENAL DISEASES

314829

*N*¹-[6-[3-(Dimethylamino)-2,2-dimethylpropoxy]pyridin-3-yl]-*N*²-hydroxyformamidine



C13 H22 N4 O2; Mol wt: 266.3428

ACTION – A representative compound from a series of hydroxyformamidine derivatives with the ability to inhibit the production of 20-HETE (IC_{50} = 0.6 nM in rat kidney microsomes). It is expected to be useful for the treatment of nephropathies, cerebrovascular diseases and circulatory diseases.

SOURCE – Taisho.

REFERENCES

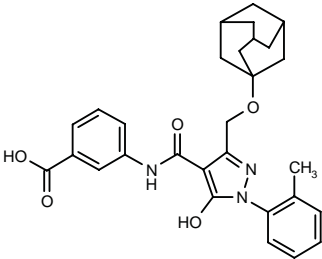
1. Sato, M. et al. (Taisho Pharmaceutical Co., Ltd.) *Hydroxyformamidine derivs. and medicines containing the same*. WO 0196309.

GASTROINTESTINAL DRUGS

ANTIULCER DRUGS

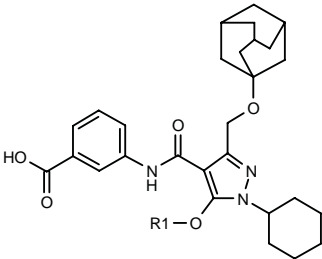
313672

3-[3-(Adamant-1-yloxymethyl)-5-hydroxy-1-(2-methyl-phenyl)-1*H*-pyrazol-4-ylcarboxamido]benzoic acid

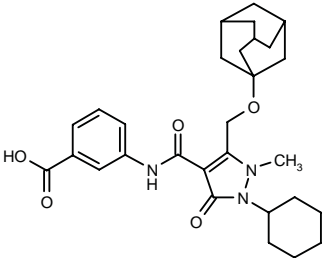


C29 H31 N3 O5; Mol wt: 501.5799

ACTION – Agent with affinity for cholecystokinin (CCK) receptors, shown to inhibit pentagastrin-induced acid secretion in immature rat stomach (pK_B = 7.72), indicating gastrin (CCK₂)-antagonist activity. Potentially useful in the treatment of gastrointestinal disorders, as well as for preventing hyperplasia associated with the administration of proton pump inhibitors. Other exemplified pyrazole derivatives are:



Compound	R1	Formula
313675	H	C ₂₈ H ₃₅ N ₃ O ₅
313676	Me	C ₂₉ H ₃₇ N ₃ O ₅



313677: C29 H37 N3 O5

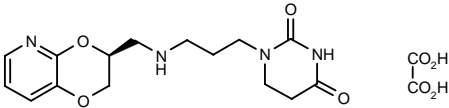
SOURCE – James Black Foundation.

REFERENCES

1. McDonald, I.M. et al. (James Black Foundation Ltd.) *Pyrazole derivs. and their use as gastrin and cholecystokinin receptor ligands*. WO 0190078.

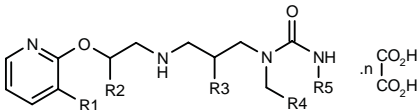
314709

(-)-1-[3-[2,3-Dihydro[1,4]dioxino[2,3-*b*]pyridin-3(*S*)-ylmethylamino]propyl]perhydropyrimidine-2,4-dione oxalate

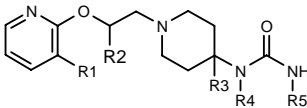


C15 H20 N4 O4 . C2 H2 O4; Mol wt: 410.3808

ACTION – Agent with fundic relaxant properties, shown to induce gastric motor activity in dogs at 0.04 mg/kg i.d. while being devoid of vasoconstrictor activity. Potentially useful for the treatment of dyspepsia, early satiety, bloating and anorexia, without undesirable cardiovascular side effects. Other exemplified compounds are:



Compound	R1,R2	R3	R4,R5	Isomer	n	Formula
314710	-OCH2-	H	-(CH2)2-		0	C ₁₅ H ₂₂ N ₄ O ₃
314711	-OCH2-	H	-(CH2)2-	(-)	1	C ₁₅ H ₂₂ N ₄ O ₃ .C ₂ H ₂ O ₄
314712	-OCH2-	H	-C(Me)2CH2-		1	C ₁₇ H ₂₆ N ₄ O ₃ .C ₂ H ₂ O ₄
314713	-OCH2-	H	-CO-		1	C ₁₄ H ₁₈ N ₄ O ₄ .C ₂ H ₂ O ₄
314715	-(CH2)2-	H	-(CH2)2-		1	C ₁₆ H ₂₄ N ₄ O ₂ .C ₂ H ₂ O ₄
314717	-O-	H	-C(Me)2CH2-		0	C ₁₆ H ₂₄ N ₄ O ₃
314718	-OCH2-	OH	-CO-		0	C ₁₄ H ₁₈ N ₄ O ₅
314723	-OCH2-	H	-CO-	S	1	C ₁₄ H ₁₈ N ₄ O ₄ .C ₂ H ₂ O ₄



Compound	R1,R2	R3	R4,R5	Isomer	Formula
314719	-OCH2-	CH2OH	-(CH2)3-	(+)	C ₁₈ H ₂₆ N ₄ O ₄
314720	-OCH2-	H	-(CH2)2-	(+)	C ₁₆ H ₂₂ N ₄ O ₃
314721	-OCH2-	H	-(CH2)3-	S	C ₁₇ H ₂₄ N ₄ O ₃
314722	-O-	H	-(CH2)2-		C ₁₅ H ₂₀ N ₄ O ₃

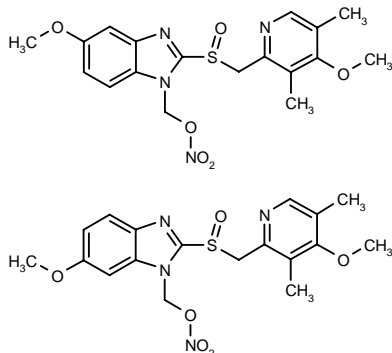
SOURCE – Janssen.

REFERENCES

1. Van Emelen, K. et al. (Janssen Pharmaceutica NV) *Cpds. for treating impaired fundic relaxation*. WO 0198306.

314862

(1:3) Mixture of [5-methoxy-2-(4-methoxy-3,5-dimethylpyridin-2-ylmethylsulfanyl)-1*H*-benzimidazol-1-yl]methyl nitrate and [6-methoxy-2-(4-methoxy-3,5-dimethylpyridin-2-yl-methylsulfanyl)-1*H*-benzimidazol-1-yl]methyl nitrate



2 C18 H20 N4 O6 S; Mol wt: 840.8880

ACTION – A nitric oxide (NO)-releasing derivative of a proton pump inhibitor, potentially useful for the treatment of *Helicobacter pylori* infections.

SOURCE – AstraZeneca.

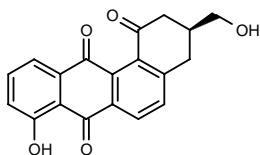
REFERENCES

1. Bergman, R. et al. (AstraZeneca AB) *New cpds. useful as antibacterial agents*. WO 0200166.

YM-181741*

301486

8-Hydroxy-3(*S*)-(hydroxymethyl)-1,2,3,4,7,12-hexahydrobenzo[*a*]anthracene-1,7,12-trione



C19 H14 O5; Mol wt: 322.3146

ACTION – Anti-*Helicobacter pylori* agent, a benz[*a*]anthraquinone isolated from the culture broth of *Streptomyces* sp. Q57219. Compound exhibited strong activity against *H. pylori* (MIC = 0.2 µg/ml) and weak or no activity against a range of Gram-positive and Gram-negative bacteria, suggesting a low potential for disturbing the microbial flora of the intestine, and thus for inducing diarrhea.

SOURCE – Yamanouchi.

REFERENCES

1. Taniguchi, M. et al. (Yamanouchi Pharmaceutical Co., Ltd.) *Benzo[*a*]anthracene-1,7,12-trione derivs*. JP 2001019656.

2. Taniguchi, M. et al. YM-181741, a novel benz[*a*]anthraquinone antibiotic with anti-*Helicobacter pylori* activity from *Streptomyces* sp. J Antibiot 2002, 55(1): 30.

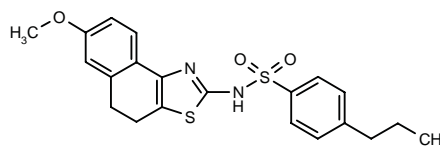
*Identified compound **301486** Drug Data Rep 2001, 023(07): 0672.

ENDOCRINE DRUGS

ANTIDIABETIC DRUGS

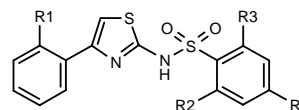
313700

N-(7-Methoxy-4,5-dihydronaphtho[1,2-*d*]thiazol-2-yl)-4-propylbenzenesulfonamide



C21 H22 N2 O3 S2; Mol wt: 414.5478

ACTION – An inhibitor of 11β-hydroxysteroid dehydrogenase type 1 (K_i = 14 nM), potentially useful for the treatment of diabetes, obesity, glaucoma, osteoporosis, cognition disorders, immune disorders and depression. Other exemplified compounds are:



Compound	R1	R2	R3	R4	Formula
313701	H	Cl	Cl	Cl	C ₁₅ H ₉ Cl ₃ N ₂ O ₂ S ₂
313702	Cl	H	H	Pr	C ₁₈ H ₁₇ ClN ₂ O ₂ S ₂

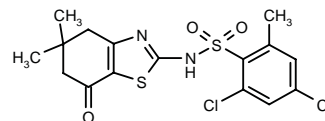
SOURCE – Biovitrum.

REFERENCES

1. Kurz, G. and Nilsson, M. (Biovitrum AB) *Inhibitors of 11-β-hydroxy steroid dehydrogenase type 1*. WO 0190092.

313703

2,4-Dichloro-*N*-(5,5-dimethyl-7-oxo-4,5,6,7-tetrahydrobenzothiazol-2-yl)-6-methylbenzenesulfonamide

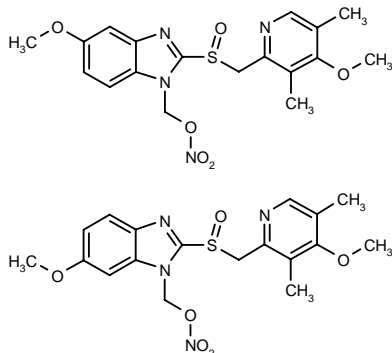


C16 H16 Cl2 N2 O3 S2; Mol wt: 419.3514

ACTION – An inhibitor of 11β-hydroxysteroid dehydrogenase type 1 (K_i = 28 nM), potentially useful for the treatment of diabetes, obesity, glaucoma, osteoporosis, cognition disorders, immune disorders and depression. Another exemplified compound is:

314862

(1:3) Mixture of [5-methoxy-2-(4-methoxy-3,5-dimethylpyridin-2-ylmethylsulfanyl)-1*H*-benzimidazol-1-yl]methyl nitrate and [6-methoxy-2-(4-methoxy-3,5-dimethylpyridin-2-yl-methylsulfanyl)-1*H*-benzimidazol-1-yl]methyl nitrate



2 C18 H20 N4 O6 S; Mol wt: 840.8880

ACTION – A nitric oxide (NO)-releasing derivative of a proton pump inhibitor, potentially useful for the treatment of *Helicobacter pylori* infections.

SOURCE – AstraZeneca.

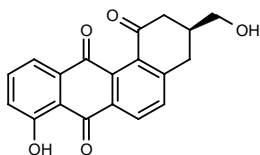
REFERENCES

1. Bergman, R. et al. (AstraZeneca AB) *New cpds. useful as antibacterial agents*. WO 0200166.

YM-181741*

301486

8-Hydroxy-3(*S*)-(hydroxymethyl)-1,2,3,4,7,12-hexahydrobenzo[*a*]anthracene-1,7,12-trione



C19 H14 O5; Mol wt: 322.3146

ACTION – Anti-*Helicobacter pylori* agent, a benz[*a*]anthraquinone isolated from the culture broth of *Streptomyces* sp. Q57219. Compound exhibited strong activity against *H. pylori* (MIC = 0.2 µg/ml) and weak or no activity against a range of Gram-positive and Gram-negative bacteria, suggesting a low potential for disturbing the microbial flora of the intestine, and thus for inducing diarrhea.

SOURCE – Yamanouchi.

REFERENCES

1. Taniguchi, M. et al. (Yamanouchi Pharmaceutical Co., Ltd.) *Benzo[*a*]anthracene-1,7,12-trione derivs*. JP 2001019656.

2. Taniguchi, M. et al. YM-181741, a novel benz[*a*]anthraquinone antibiotic with anti-*Helicobacter pylori* activity from *Streptomyces* sp. J Antibiot 2002, 55(1): 30.

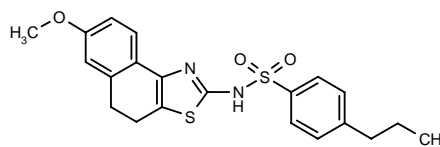
*Identified compound **301486** Drug Data Rep 2001, 023(07): 0672.

ENDOCRINE DRUGS

ANTIDIABETIC DRUGS

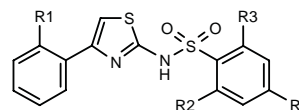
313700

N-(7-Methoxy-4,5-dihydronaphtho[1,2-*d*]thiazol-2-yl)-4-propylbenzenesulfonamide



C21 H22 N2 O3 S2; Mol wt: 414.5478

ACTION – An inhibitor of 11β-hydroxysteroid dehydrogenase type 1 (K_i = 14 nM), potentially useful for the treatment of diabetes, obesity, glaucoma, osteoporosis, cognition disorders, immune disorders and depression. Other exemplified compounds are:



Compound	R1	R2	R3	R4	Formula
313701	H	Cl	Cl	Cl	C ₁₅ H ₉ Cl ₃ N ₂ O ₂ S ₂
313702	Cl	H	H	Pr	C ₁₈ H ₁₇ ClN ₂ O ₂ S ₂

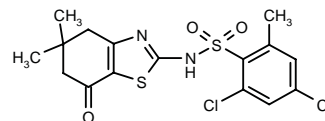
SOURCE – Biovitrum.

REFERENCES

1. Kurz, G. and Nilsson, M. (Biovitrum AB) *Inhibitors of 11-β-hydroxy steroid dehydrogenase type 1*. WO 0190092.

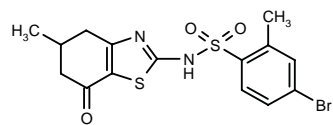
313703

2,4-Dichloro-*N*-(5,5-dimethyl-7-oxo-4,5,6,7-tetrahydrobenzothiazol-2-yl)-6-methylbenzenesulfonamide



C16 H16 Cl2 N2 O3 S2; Mol wt: 419.3514

ACTION – An inhibitor of 11β-hydroxysteroid dehydrogenase type 1 (K_i = 28 nM), potentially useful for the treatment of diabetes, obesity, glaucoma, osteoporosis, cognition disorders, immune disorders and depression. Another exemplified compound is:



313704: C15 H15 Br N2 O3 S2

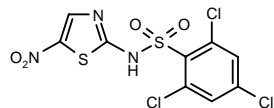
SOURCE – Biovitrum.

REFERENCES

1. Barf, T. et al. (Biovitrum AB) *Inhibitors of 11-β-hydroxy steroid dehydrogenase type 1*. WO 0190094.

313705

2,4,6-Trichloro-*N*-(5-nitrothiazol-2-yl)benzenesulfonamide



C9 H4 Cl3 N3 O4 S2; Mol wt: 388.6386

ACTION – A representative compound from a series of inhibitors of 11β-hydroxysteroid dehydrogenase type 1 with a K_i of 545 nM for inhibition of the enzyme. Potentially useful for the treatment of diabetes, obesity, glaucoma, osteoporosis, cognition disorders, immune disorders and depression.

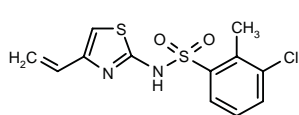
SOURCE – Biovitrum.

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1. Nilsson, M. (Biovitrum AB) *Inhibitors of 11-β-hydroxy steroid dehydrogenase type 1*. WO 0190093.

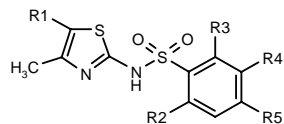
313706

3-Chloro-2-methyl-*N*-(4-vinylthiazol-2-yl)benzenesulfonamide



C12 H11 Cl N2 O2 S2; Mol wt: 314.8159

ACTION – An inhibitor of 11β-hydroxysteroid dehydrogenase type 1 (K_i = 90 nM), potentially useful for the treatment of diabetes, obesity, glaucoma, osteoporosis, cognition disorders, immune disorders and depression. Other exemplified compounds are:



Compound	R1	R2	R3	R4	R5	Formula
313708	H	H	Me	Cl	H	C ₁₁ H ₁₁ ClN ₂ O ₂ S ₂
313709	CH2C(Cl)3	Cl	Cl	H	Cl	C ₁₂ H ₈ Cl ₆ N ₂ O ₂ S ₂
313710	Ac	H	H	H	3-Cl-4-CN-PhO	C ₁₉ H ₁₄ ClN ₃ O ₄ S ₂

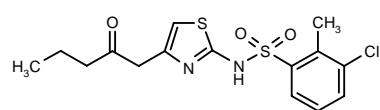
SOURCE – Biovitrum.

REFERENCES

1. Barf, T. et al. (Biovitrum AB) *Inhibitors of 11-β-hydroxy steroid dehydrogenase type 1*. WO 0190091.

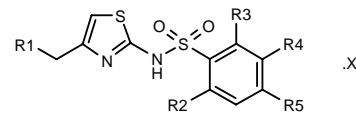
313712

3-Chloro-2-methyl-*N*-[4-(2-oxopentyl)thiazol-2-yl]-benzenesulfonamide



C15 H17 Cl N2 O3 S2; Mol wt: 372.8953

ACTION – An inhibitor of 11β-hydroxysteroid dehydrogenase type 1 (K_i = 14 nM), potentially useful for the treatment of diabetes, obesity, glaucoma, osteoporosis, cognition disorders, immune disorders and depression. Other exemplified compounds include the following:



Compound	R1	R2	R3	R4	R5	X	Formula
313714	4-morpholinyl-CO	Cl	Cl	H	Cl		C ₁₅ H ₁₄ Cl ₃ N ₃ O ₄ S ₂
313715	4-morpholinyl-CO	H	H	H	Ph		C ₂₁ H ₂₁ N ₃ O ₄ S ₂
313716	CH2OH	H	Me	Cl	H		C ₁₂ H ₁₃ ClN ₂ O ₃ S ₂
313717	3-Pyr-OCH2	H	Me	Cl	H		C ₁₇ H ₁₆ ClN ₃ O ₃ S ₂
313718	4-morpholinyl-CH2	H	Me	Cl	H	HCl	C ₁₆ H ₂₀ ClN ₃ O ₃ S ₂ .HCl

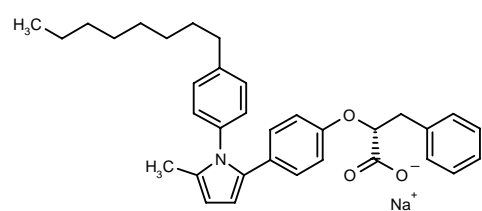
SOURCE – Biovitrum.

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1. Barf, T. et al. (Biovitrum AB) *Inhibitors of 11-β-hydroxy steroid dehydrogenase type 1*. WO 0190090.

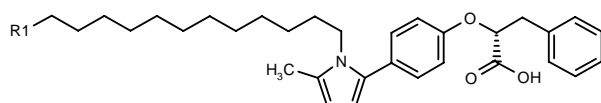
313933

2(*R*)-[4-[5-Methyl-1-(4-octylphenyl)-1 *H*-pyrrol-2-yl]phenoxy]-3-phenylpropionic acid sodium salt



C34 H38 N Na O3; Mol wt: 531.6682

ACTION – Protein-tyrosine-phosphatase inhibitor with an IC_{50} of 0.09 μM against PTP1B, for use in the treatment of diabetes. Other exemplified compounds are:



Compound	R1	Formula
313934	H	C ₃₂ H ₄₃ NO ₃
313935	Me	C ₃₃ H ₄₆ NO ₃

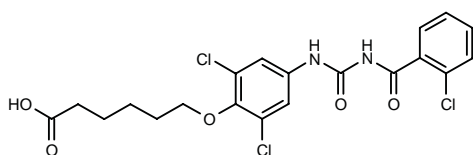
SOURCE – Takeda.

REFERENCES

1. Matsumoto, T. et al. (Takeda Chemical Industries, Ltd.) *Tyrosine phosphatase inhibitors*. WO 0190067.

314258

6-[2,6-Dichloro-4-[3-(2-chlorobenzoyl)ureido]phenoxy]-hexanoic acid



C₂₀ H₁₉ Cl₃ N₂ O₅; Mol wt: 473.7381

ACTION – Acylphenylurea inhibitor of glycogen phosphorylase (87% inhibition at 10 μ M), potentially useful for the treatment of type 2 diabetes.

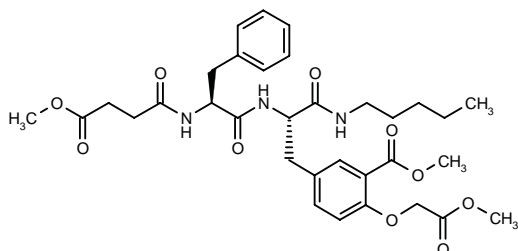
SOURCE – Aventis Pharma.

REFERENCES

1. Defossa, E. et al. (Aventis Pharma Deutschland GmbH) *Acylphenyl urea derivs., methods for the production thereof and use thereof as a medicament*. WO 0194300.

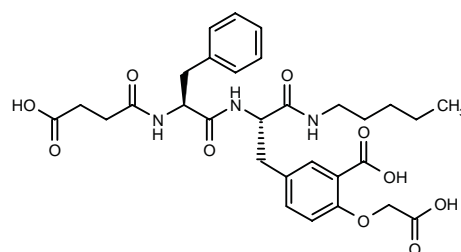
314657

N-(4-Methoxysuccinyl)-L-phenylalanyl-3-(methoxycarbonyl)-*O*-(2-methoxy-2-oxoethyl)-*N*-pentyl-L-tyrosinamide



C₃₃ H₄₃ N₃ O₁₀; Mol wt: 641.7137

ACTION – Prodrug ester of the potent and competitive protein-tyrosine-phosphatase PTP1B inhibitor **314658** (K_i = 0.22 μ M), proven to increase basal 2-deoxyglucose uptake into L6 myocytes, as well as insulin-resistant 3T3-L1 adipocytes. In these cells, the prodrug also increased tyrosine phosphorylation of the insulin receptor and insulin receptor substrate-1 (IRS-1). Potentially useful for the treatment of type 2 diabetes.



314658: C₃₀ H₃₇ N₃ O₁₀

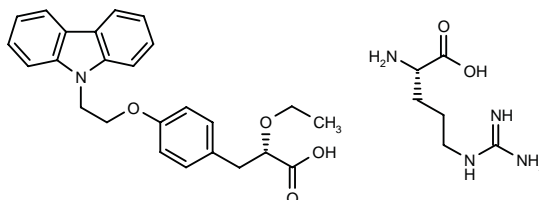
SOURCES – Biovitrum; Pharmacia.

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1. Larsen, S.D. et al. (Pharmacia & Upjohn Co.) *Inhibitors of protein tyrosine phosphatase*. JP 2001514245, US 6353023, WO 9911606.
2. Bleasdale, J.E. et al. *Small molecule peptidomimetics containing a novel phosphotyrosine bioisostere inhibit protein tyrosine phosphatase 1B and augment insulin action*. Biochemistry 2001, 40(19): 5642.
3. Larse, S.D. et al. *Synthesis and biological activity of a novel class of small molecular weight peptidomimetic competitive inhibitors of protein tyrosine phosphatase 1B*. J Med Chem 2002, 45(3): 598.

314996

3-[4-[2-(9*H*-Carbazol-9-yl)ethoxy]phenyl]-2(*S*)-ethoxy-propionic acid arginine salt



C₂₅ H₂₅ N₄ O₄ . C₆ H₁₄ N₄ O₂; Mol wt: 577.6781

ACTION – Dual agonist of peroxisome proliferator-activated receptors PPAR α and PPAR γ (EC_{50} = 0.36 and 0.17 μ M, respectively) with no activity at PPAR δ or retinoic acid receptor RAR α receptors. In diabetic *db/db* mice, it reduced blood glucose and triglyceride levels (ED_{50} = 0.27 and 0.52 mg/kg p.o., respectively) and improved insulin sensitivity (ED_{50} = 0.34 mg/kg p.o.). The compound also dose-dependently reduced serum triglycerides (ED_{50} = 0.06 mg/kg) and total cholesterol levels (ED_{50} = 0.34 mg/kg) in cholesterol-fed rats when given orally for the last 4 days of a high-cholesterol diet. Its favorable pharmacokinetics in mice and rats. i.e., long plasma half-life, high AUC and low clearance, contribute to its superior *in vivo* efficacy compared to pioglitazone and rosiglitazone. Potentially useful for the treatment of type 2 diabetes.

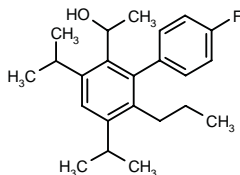
SOURCES – Dr. Reddy's Research Foundation; Novo Nordisk.

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1. Jeppesen, L. et al. (Novo Nordisk A/S; Dr. Reddy's Research Foundation) *New cpds., their preparation and use*. EP 1123279, WO 0023425.
2. Sauerberg, P. et al. *Novel tricyclic- α -alkyloxyphenylpropionic acids: Dual PPAR α/γ agonists with hypolipidemic and antidiabetic activity*. J Med Chem 2002, 45(4): 789.

BAY-27-9955**277264**

(+)-1-(4'-Fluoro-3,5-diisopropyl-6-propylbiphenyl-2-yl)-ethanol



C23 H31 F O; Mol wt: 342.4949

ACTION – Competitive nonpeptide antagonist of the glucagon receptor with high selectivity for human and dog receptors (IC_{50} = 110 and 140 nM, respectively) over mouse, rabbit and rat receptors (IC_{50} = 400, 700 and 8000 nM, respectively), GLP-1 and a variety of other receptors; it inhibited glucagon-stimulated cAMP generation with an IC_{50} of 46 nM and a pA_2 of 7.8. Pharmacokinetic studies in rats showed rapid absorption after oral administration, with 40% oral bioavailability. In an early clinical trial in healthy subjects, compound given as single oral doses of 70 and 200 mg to fasted subjects prior to infusion of somatostatin, insulin and glucagon strongly attenuated the hyperglucagonemia, glucose production and plasma glucose levels increased by hormones. Compound was well tolerated at the tested doses. Potentially useful for the treatment of type 2 diabetes.

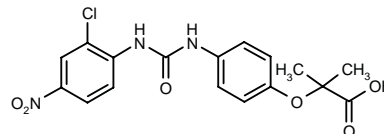
SOURCE – Bayer.

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1. Schmidt, G. et al. (Bayer AG;Bayer Corp.) *Substd. pyridines and biphenyls as anti-hypercholesterinemic, anti-hyperlipoproteinemic and anti-hyperglycemic agents*. WO 9804528.
2. Schoen, W.R. et al. (Bayer Corp.;Bayer AG) *Substd. biphenyls*. US 6218431.
3. Bjorge, S. et al. *BAY 27-9955: Plasma pharmacokinetics in Sprague-Dawley rats following intravenous and oral administration*. Diabetes 1999, 48(Suppl. 1): Abst 2003.
4. Livingston, J.N. et al. *BAY 27-9955, a novel, non-peptide antagonist of glucagon binding to the glucagon receptor*. Diabetes 1999, 48(Suppl. 1): Abst 0862.
5. Perrino, P. and Sarah, J. *[14C]BAY 27-9955; distribution of radioactivity and elimination after single oral administration to rats*. Diabetes 1999, 48(Suppl. 1): Abst 2001.
6. Petersen, K.F. and Sullivan, J.T. *Effects of a novel glucagon receptor antagonist (Bay 27-9955) on glucagon-stimulated glucose production in humans*. Diabetologia 2001, 44(11): 2018.
7. Petersen, K.F. et al. *The effects of a specific glucagon antagonist on glucagon stimulated glucose production*. Diabetologia 1999, 42(Suppl. 1): Abst 150.
8. *New antidiabetic agent presented by Bayer scientists this week in San Diego*. DailyDrugNews.com (Daily Essentials) 1999, June 21.

TREATMENT OF DIABETIC COMPLICATIONS**LR-33****314584**

2-[4-[3-(2-Chloro-4-nitrophenyl)ureido]phenoxy]-2-methylpropionic acid



C17 H16 Cl N3 O6; Mol wt: 393.7814

ACTION – A representative compound from a series of phenoxy-substituted isobutyric acids with the ability to inhibit the glycation of proteins and thus the formation of advanced glycation end products (AGEs). Compound prevented crosslinking of glycated BSA to rat tail tendon collagen by 61% at 1 mM. Potentially useful for slowing the progression of diabetic complications, as well as age-related disorders such as rheumatoid arthritis, Alzheimer's disease, uremia, neurotoxicity and atherosclerosis.

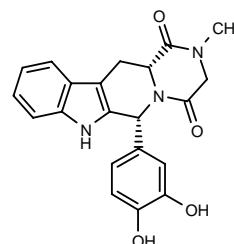
SOURCE – City of Hope National Medical Center, Duarte, CA (US).

REFERENCES

1. Rahbar, S. and Lalezari, I. (City of Hope National Medical Center) *Inhibitors of formation of advanced glycation endproducts (AGEs)*. US 6337350.

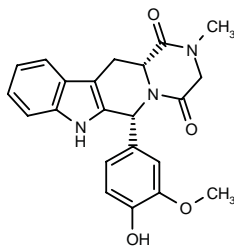
TREATMENT OF MALE SEXUAL DYSFUNCTION**314259**

(6*R*,12*aR*)-6-(3,4-Dihydroxyphenyl)-2-methyl-1,2,3,4,6,7,12,12a-octahydropyrazino[1',2':1,6]pyrido[3,4-*b*]indole-1,4-dione



C21 H19 N3 O4; Mol wt: 377.3981

ACTION – Phosphodiesterase type 5 (PDE5) inhibitor (IC_{50} = 5 nM), potentially useful for the treatment of male erectile dysfunction and female arousal disorders, as well as other disorders mediated by cGMP-specific phosphodiesterases including angina pectoris, hypertension, chronic obstructive pulmonary disease, acute respiratory distress syndrome, congestive heart failure, renal failure, atherosclerosis, inflammation, myocardial infarction, stroke, etc. Another exemplified pyrazino[1':2':1,6]pyrido-[3,4-*b*]indole derivative is:



314260: C22 H21 N3 O4

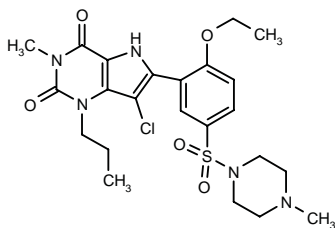
SOURCE – Lilly Icos.

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1. Orme, M.W. et al. (Lilly Icos LLC) *Tetracyclic diketopiperazine cpds. as PDEV inhibitors*. WO 0194347.

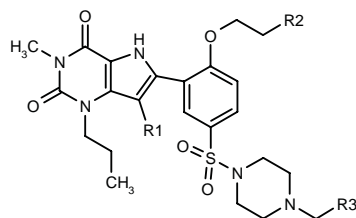
314340

7-Chloro-6-[2-ethoxy-5-(4-methylpiperazin-1-ylsulfonyl)-phenyl]-3-methyl-1-propyl-2,3,4,5-tetrahydro-1*H*-pyrrolo-[3,2-*d*]pyrimidine-2,4-dione



C23 H30 Cl N5 O5 S; Mol wt: 524.0390

ACTION – A selective inhibitor of phosphodiesterase type 5 (PDE5; IC_{50} = 3.4 nM), potentially useful for the treatment of angina, hypertension, pulmonary hypertension, congestive heart failure, renal failure, atherosclerosis, peripheral vascular disease, stroke, bronchitis, asthma, allergic rhinitis, glaucoma, male erectile dysfunction and female sexual dysfunction. Other exemplified pyrrolopyrimidine-2,4-dione derivatives are:



Compound	R1	R2	R3	Formula
314342	H	Me	H	C ₂₄ H ₃₃ N ₅ O ₅ S
314343	H	Me	Me	C ₂₅ H ₃₅ N ₅ O ₅ S
314346	Cl	Me	H	C ₂₄ H ₃₂ ClN ₅ O ₅ S
314347	Cl	Me	Me	C ₂₅ H ₃₄ ClN ₅ O ₅ S
314348	Cl	Me	CH ₂ OH	C ₂₅ H ₃₄ ClN ₅ O ₆ S
314349	Br	H	CH ₂ CH ₂ OH	C ₂₅ H ₃₄ BrN ₅ O ₆ S
314350	Br	Me	H	C ₂₄ H ₃₂ BrN ₅ O ₅ S
314351	Br	Me	CH ₂ OH	C ₂₅ H ₃₄ BrN ₅ O ₆ S
314352	Br	Me	CH ₂ CH ₂ OH	C ₂₆ H ₃₆ BrN ₅ O ₆ S

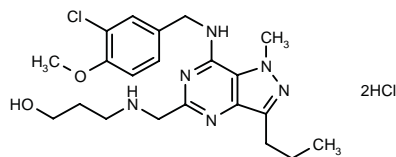
SOURCE – Almirall Prodesfarma.

REFERENCES

1. Vidal Juan, B. et al. (Almirall Prodesfarma, SA) *6-Phenylpyrrolopyrimidinedione derivs*. WO 0194350.

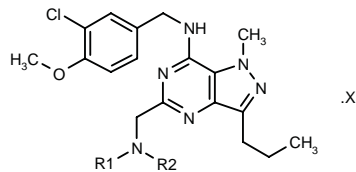
314938

3-[7-(3-Chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-ylmethylamino]-propan-1-ol dihydrochloride



C21 H29 Cl N6 O2 . 2HCl; Mol wt: 505.8749

ACTION – Phosphodiesterase type 5 (PDE5) inhibitor, potentially useful for the treatment of cardiovascular disorders and erectile dysfunction. Other exemplified 5-aminoalkyl-pyrazolo[4,3-*d*]pyrimidines are:



Compound	R1	R2	X	Formula
314943	-CH ₂ CH ₂ CH(OH)CH ₂ CH ₂ -		2HCl	C ₂₃ H ₃₁ ClN ₆ O ₂ ·2HCl
314945	CH ₂ CH ₂ OH	H	2HCl	C ₂₀ H ₂₇ ClN ₆ O ₂ ·2HCl
314946	-CH ₂ CH ₂ N(CH ₂ CH ₂ OH)CH ₂ CH ₂ -		3HCl	C ₂₄ H ₃₄ ClN ₇ O ₂ ·3HCl
314947	(CH ₂) ₃ OMe	H	2HCl	C ₂₂ H ₃₁ ClN ₆ O ₂ ·2HCl
314948	CH ₂ CH ₂ N(Me) ₂	H	3HCl	C ₂₂ H ₃₂ ClN ₇ O·3HCl

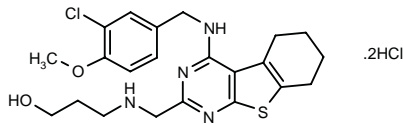
SOURCE – Merck KGaA.

REFERENCES

1. Jonas, R. et al. (Merck Patent GmbH) *5-Aminoalkyl-pyrazolo[4,3-d]pyrimidines with a phosphodiesterase V-inhibiting effect*. DE 10031584, WO 0200660.

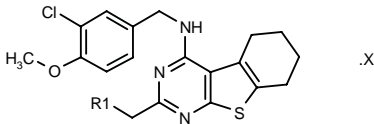
314949

3-[4-(3-Chloro-4-methoxybenzylamino)-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidin-2-ylmethyl-amino]propan-1-ol dihydrochloride



C22 H27 Cl N4 O2 S . 2HCl; Mol wt: 519.9221

ACTION – Phosphodiesterase type 5 (PDE5) inhibitor, potentially useful for the treatment of cardiovascular disorders and erectile dysfunction. Other exemplified 2-aminoalkyl-thieno[2,3-*d*]pyrimidines are:



Compound	R1	X	Formula
314950	N(CH2CH2OH)2	HCl	C23H29ClN4O3S.HCl
314951	4-OH-1-Pip	HCl	C24H29ClN4O2S.HCl
314953	NH(CH2)3OMe	2HCl	C23H29ClN4O2S.2HCl
314954	NHCH2CH2OH	2HCl	C21H25ClN4O2S.2HCl
314958	NH(CH2)3N(Me)2	fumarate	C24H32ClN5OS.C4H4O4
314960	4-(CH2CH2OH)-1-Piz	2HCl	C25H32ClN5O2S.2HCl

SOURCE – Merck KGaA.

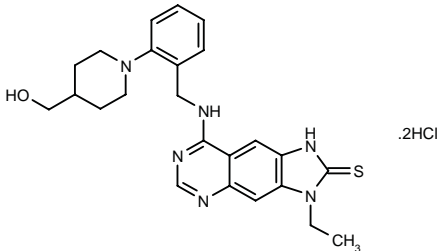
REFERENCES

1. Jonas, R. et al. (Merck Patent GmbH) 2-Aminoalkyl-thieno[2,3-*d*]pyrimidines. DE 10031585, WO 0200664.

KF-31327

315009

3-Ethyl-8-[2-[4-(hydroxymethyl)piperidin-1-yl]benzyl-amino]-2,3-dihydro-1*H*-imidazo[4,5-*g*]quinazoline-2-thione dihydrochloride



C24 H28 N6 O S . 2HCl; Mol wt: 521.5140

ACTION – Potent inhibitor of phosphodiesterase type 5 (PDE5; IC₅₀ = 0.074 nM) with more than 500-fold selectivity over PDE1, PDE2, PDE3 and PDE4 (IC₅₀ = 380, 670, 38 and 800 nM, respectively). Compound inhibited PDE5 in a noncompetitive manner and was 45-fold more potent against PDE5 than sildenafil (K_i = 0.16 and 7.2 nM, respectively). In the presence of nitroglycerin, both title compound and sildenafil inhibited collagen-induced rabbit platelet aggregation (58 and 50%, respectively, at 0.1 μM) by augmenting the intracellular levels of cGMP, without affecting cAMP. In the absence of nitroglycerin, platelet aggregation was inhibited only at higher concentrations of compound and both cGMP and cAMP were increased; sildenafil 10 μM had no effect. Potentially useful for the treatment of disorders including erectile dysfunction.

SOURCE – Kyowa Hakko.

REFERENCES

- Fujino, K. et al. (Kyowa Hakko Kogyo Co., Ltd.) Preparation method of imidazoquinazoline derivs. JP 1999005794.
- Onoda, Y. et al. (Kyowa Hakko Kogyo Co., Ltd.) Imidazoquinazoline derivs. EP 0863144, WO 9808848.
- Fujino, K. et al. Development of a practical synthetic route of a PDE V inhibitor KF31327. Org Process Res Dev 2001, 5(4): 426.
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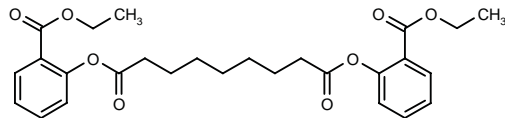
DERMATOLOGIC DRUGS

ACNE THERAPY

TU-2100

297136

Nonanedioic acid bis[2-(ethoxycarbonyl)phenyl] diester

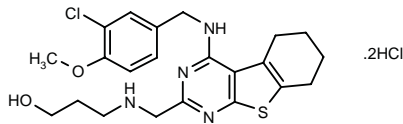


C27 H32 O8; Mol wt: 484.5418

ACTION – Antiacne prodrug composed of azelaic acid and salicylate (as ethyl ester) that is slowly hydrolyzed to the active agents in the skin.

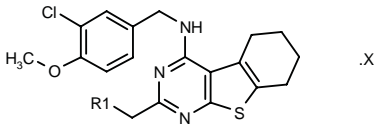
314949

3-[4-(3-Chloro-4-methoxybenzylamino)-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidin-2-ylmethyl-amino]propan-1-ol dihydrochloride



C22 H27 Cl N4 O2 S . 2HCl; Mol wt: 519.9221

ACTION – Phosphodiesterase type 5 (PDE5) inhibitor, potentially useful for the treatment of cardiovascular disorders and erectile dysfunction. Other exemplified 2-aminoalkyl-thieno[2,3-*d*]pyrimidines are:



Compound	R1	X	Formula
314950	N(CH2CH2OH)2	HCl	C ₂₃ H ₂₉ ClN ₄ O ₃ S.HCl
314951	4-OH-1-Pip	HCl	C ₂₄ H ₂₉ ClN ₄ O ₂ S.HCl
314953	NH(CH2)3OMe	2HCl	C ₂₃ H ₂₉ ClN ₄ O ₂ S.2HCl
314954	NHCH2CH2OH	2HCl	C ₂₁ H ₂₅ ClN ₄ O ₂ S.2HCl
314958	NH(CH2)3N(Me)2	fumarate	C ₂₄ H ₃₂ ClN ₅ OS.C ₄ H ₄ O ₄
314960	4-(CH2CH2OH)-1-Piz	2HCl	C ₂₅ H ₃₂ ClN ₅ O ₂ S.2HCl

SOURCE – Merck KGaA.

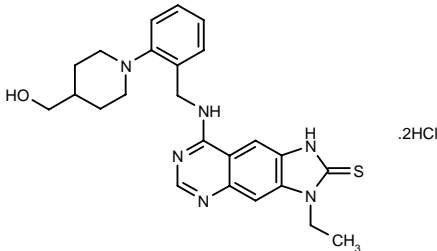
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KF-31327

315009

3-Ethyl-8-[2-[4-(hydroxymethyl)piperidin-1-yl]benzyl-amino]-2,3-dihydro-1*H*-imidazo[4,5-*g*]quinazoline-2-thione dihydrochloride



C24 H28 N6 O S . 2HCl; Mol wt: 521.5140

ACTION – Potent inhibitor of phosphodiesterase type 5 (PDE5; IC₅₀ = 0.074 nM) with more than 500-fold selectivity over PDE1, PDE2, PDE3 and PDE4 (IC₅₀ = 380, 670, 38 and 800 nM, respectively). Compound inhibited PDE5 in a noncompetitive manner and was 45-fold more potent against PDE5 than sildenafil (K_i = 0.16 and 7.2 nM, respectively). In the presence of nitroglycerin, both title compound and sildenafil inhibited collagen-induced rabbit platelet aggregation (58 and 50%, respectively, at 0.1 μM) by augmenting the intracellular levels of cGMP, without affecting cAMP. In the absence of nitroglycerin, platelet aggregation was inhibited only at higher concentrations of compound and both cGMP and cAMP were increased; sildenafil 10 μM had no effect. Potentially useful for the treatment of disorders including erectile dysfunction.

SOURCE – Kyowa Hakko.

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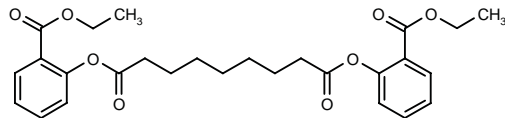
DERMATOLOGIC DRUGS

ACNE THERAPY

TU-2100

297136

Nonanedioic acid bis[2-(ethoxycarbonyl)phenyl] diester



C27 H32 O8; Mol wt: 484.5418

ACTION – Antiacne prodrug composed of azelaic acid and salicylate (as ethyl ester) that is slowly hydrolyzed to the active agents in the skin.

SOURCES – Istituto Biochimico Italiano Giovanni Lorenzini; Tamarkin.

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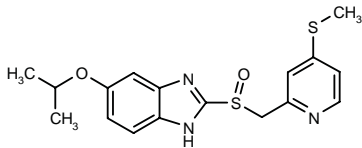
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TREATMENT OF ALLERGIC SKIN DISORDERS

TU-572

297811

5-Isopropoxy-2-[4-(methylsulfanyl)pyridin-2-ylmethylsulfanyl]-1*H*-benzimidazole



C17 H19 N3 O2 S2; Mol wt: 361.4881

ACTION – Potent and selective inhibitor of CD45 protein-tyrosine-phosphatase (PTPase), proven to strongly and concentration-dependently inhibit IgE-mediated histamine release from rat peritoneal mast cells, with a similar effect to tranilast. In mice, compound dose-dependently (3-10 mg/kg s.c.) inhibited the passive cutaneous anaphylaxis (PCA) reaction, with efficacy superior to tranilast. In a mouse model of contact hypersensitivity induced by TNCB, doses of 10 and 30 mg/kg s.c. reduced ear swelling, serum IgE levels and markedly inhibited IL-4 production. Potentially useful for the treatment of allergic skin disorders.

SOURCES – Institute of Physical and Chemical Research (RIKEN), Saitama (JP); Taisho.

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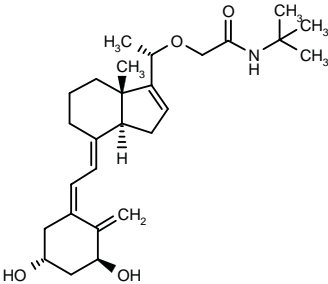
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ANTIPSORIATICS

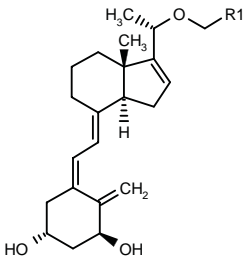
314835

N-*tert*-Butyl-2-[1 α ,3 β -dihydroxy-9,10-secopregna-5(*Z*),7(*E*),10,16-tetraen-20(*S*)-yloxy]acetamide



C27 H41 N O4; Mol wt: 443.6239

ACTION – Antiproliferative vitamin D analogue with potential in the treatment of dermatoses such as psoriasis, and having low hypercalcemic activity. This compound was 7-fold more active than 1 α ,25-dihydroxy-vitamin D₃ in inhibiting the proliferation of human keratinocytes. Other exemplified compounds are:



Compound	R1	Formula
314836	t-BuOCO	C ₂₇ H ₄₀ O ₅
314837	t-BuN(Me)CO	C ₂₈ H ₄₃ NO ₄
314838	t-BuOCOCH2	C ₂₈ H ₄₂ O ₅
314839	i-PrOCO	C ₂₆ H ₃₈ O ₅

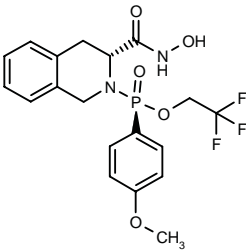
SOURCE – Chugai.

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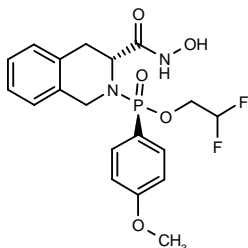
314988

(*R_p*)-[3(*R*)-(N-Hydroxycarbamoyl)-1,2,3,4-tetrahydroisoquinolin-2-yl](4-methoxyphenyl)phosphinic acid 2,2,2-trifluoroethyl ester



C19 H20 F3 N2 O5 P; Mol wt: 444.3440

ACTION – Antipsoriatic antedrug, proven to inhibit the epidermal growth factors (EGFs) amphiregulin ($IC_{50} = 0.73 \mu M$) and heparin-binding EGF-like growth factor (HB-EGF; $IC_{50} = 0.95 \mu M$), and matrix metalloproteinases MMP-1 (interstitial collagenase; $K_i = 6.57 nM$), MMP-3 (stromelysin 1; $K_i = 6.75$) and MMP-9 (gelatinase B; $K_i = 3.68 nM$). Compound was completely degraded in human plasma with a $t_{1/2}$ of < 1 min. In a murine model of TPA-induced epidermal hyperplasia, it significantly decreased epidermal thickness by 81.3% at 100 $\mu g/head$ topically. Another related compound is:



314991: C19 H21 F2 N2 O5 P

SOURCE – Nippon Organon.

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PIMECROLIMUS

Prop INN, USAN

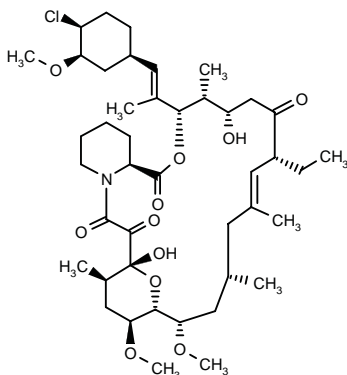
175619

[1*R*,9*S*,12*S*(1'*R*,3'*R*,4'*S*),13*R*,14*S*,17*R*,21*S*,23*S*,24*R*,25*S*,27*R*]-12-[2-(4-Chloro-3-methoxycyclohexyl)-1(*E*)-methylvinyl]-17-ethyl-1,14-dihydroxy-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxo-4-azatricyclo-[22.3.1.0^{4,9}]octacos-18(*E*)-ene-2,3,10,16-tetraone

[3*S*(1'*R*,3'*R*,4'*S*),4*R*,5*S*,8*R*,9*E*,12*S*,14*S*,15*R*,16*S*,18*R*,19*R*,26*aS*]-3-[2-(4-Chloro-3-methoxycyclohexyl)-1(*E*)-methylvinyl]-15,19-epoxy-8-ethyl-15,19-dihydroxy-14,16-dimethoxy-4,10,12,18-tetramethyl-1,4,5,6,7,8,11,12,13,14,15,16,17,18,19,20,21,23,24,25,26,26a-docosahydro-3*H*-pyrido[2,1-*c*][1,4]oxaazacyclotricosine-1,7,20,21-tetraone

ASM-981

SDZ-ASM-981⁺



C43 H68 Cl N O11; Mol wt: 810.4592

ACTION – Nonsteroidal skin-selective inflammatory cytokine inhibitor, an ascomycin derivative.

INDICATION – Short-term and intermittent long-term treatment of mild to moderate atopic dermatitis in nonimmunocompromised patients aged 2 years and over, in whom the use of alternative conventional therapies is deemed inadvisable because of potential risks, or in patients not responding adequately to or intolerant of such therapies.

PRESENTATION – Cream, 1%.

PROPRIETARY NAME – Elidel (US).

SOURCE – Novartis.

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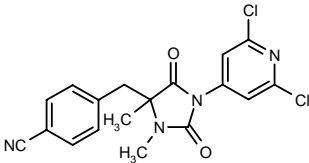
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TR-15170

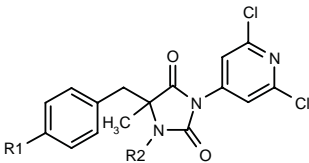
314087

4-[1-(2,6-Dichloropyridin-4-yl)-3,4-dimethyl-2,5-dioxo-imidazolidin-4-ylmethyl]benzonitrile



C18 H14 Cl2 N4 O2; Mol wt: 389.2406

ACTION – An inhibitor of $\alpha_L\beta_2$ integrin (LFA-1, CD11a/CD18)-mediated cell adhesion with potential in the treatment of psoriasis, rheumatoid arthritis, inflammatory bowel diseases, systemic lupus erythematosus, atopic dermatitis, Sjögren’s syndrome and transplant rejection. Other specifically claimed imidazolidine-2,4-dione derivatives are:



Compound	R1	R2	Formula
314088	Br	Me	C ₁₇ H ₁₄ BrCl ₂ N ₃ O ₂
314089	OPr	Me	C ₂₀ H ₂₁ Cl ₂ N ₃ O ₃
314090	OEt	Me	C ₁₉ H ₁₉ Cl ₂ N ₃ O ₃
314091	OCF ₃	Me	C ₁₈ H ₁₄ Cl ₂ F ₃ N ₃ O ₃
314092	OCF ₃	H	C ₁₇ H ₁₂ Cl ₂ F ₃ N ₃ O ₃
314093	CN	H	C ₁₇ H ₁₂ Cl ₂ N ₄ O ₂

SOURCE – Tanabe Seiyaku.

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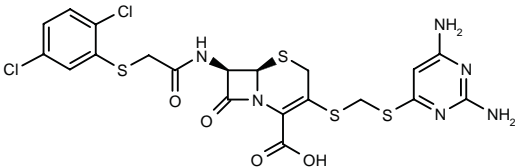
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ANTIINFECTIVE THERAPY

ANTIBIOTICS

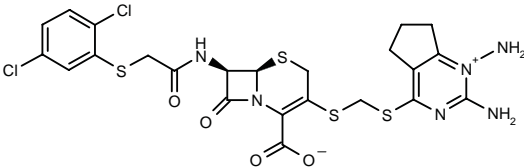
314884

(6*R*,7*R*)-3-(2,6-Diaminopyrimidin-4-ylsulfanylmethyl-sulfanyl)-7-[2-(2,5-dichlorophenylsulfanyl)acetamido]-3-cephem-4-carboxylic acid



C20 H18 Cl2 N6 O4 S4; Mol wt: 605.5702

ACTION – Cephalosporin antibiotic, particularly useful against MRSA (methicillin-resistant *Staphylococcus aureus*) bacterial strains. It gave MIC values of < 0.008, 0.063, 1, 0.063 and 0.25 $\mu\text{g/ml}$, respectively, against *S. aureus* Giorgio, *S. aureus* 77, *S. aureus* 241, *Staphylococcus epidermidis* R005 and *Enterococcus faecalis* L239 strains. Another exemplified 3-cephem-4-carboxylic acid is:



314885: C23 H22 Cl2 N6 O4 S4

SOURCE – LG Chem.

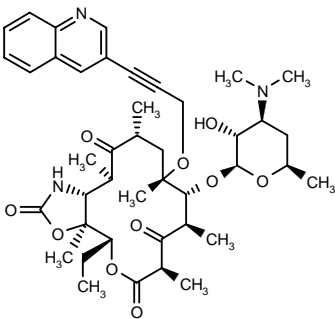
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A-217213

312525

11-Amino-11-deoxy-3-des(hexopyranosyloxy)-3-oxo-6-*O*-[3-(3-quinolinyl)-2-propynyl]erythromycin A 11-*N*,12-*O*-cyclic carbamate



C42 H57 N3 O10; Mol wt: 763.9233

ACTION – Ketolide antibiotic with excellent antibacterial activity against community-acquired respiratory tract pathogens including sensitive and resistant strains of *Streptococcus pneumoniae* (MIC₉₀ = 0.004-0.12 $\mu\text{g/ml}$), *Staphylococcus aureus* (MIC₉₀ = 0.03 $\mu\text{g/ml}$), *Haemophilus influenzae* (MIC₉₀ = 2 $\mu\text{g/ml}$) and *Moraxella catarrhalis* (MIC = 0.12 $\mu\text{g/ml}$). *In vivo*, compound was at least as effective as telithromycin or azithromycin in protecting mice from lethal systemic infections caused by *S. aureus*, *S. pneumoniae* and *H. influenzae* (ED₅₀ = 11.1, 4.6 and 43.1 mg/kg/day p.o., respectively).

SOURCE – Abbott.

REFERENCES

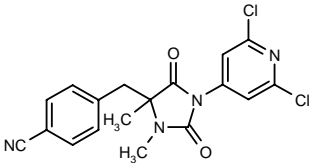
1. Or, Y.S. et al. (Abbott Laboratories Inc.) *6-*O*-Substd. ketolides having antibacterial activity*. EP 0929563, JP 2001500855, US 5866549, WO 9809978.

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TR-15170

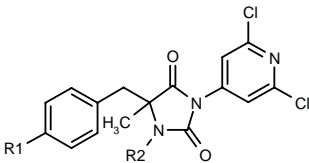
314087

4-[1-(2,6-Dichloropyridin-4-yl)-3,4-dimethyl-2,5-dioxo-imidazolidin-4-ylmethyl]benzonitrile



C18 H14 Cl2 N4 O2; Mol wt: 389.2406

ACTION – An inhibitor of $\alpha_L\beta_2$ integrin (LFA-1, CD11a/CD18)-mediated cell adhesion with potential in the treatment of psoriasis, rheumatoid arthritis, inflammatory bowel diseases, systemic lupus erythematosus, atopic dermatitis, Sjögren’s syndrome and transplant rejection. Other specifically claimed imidazolidine-2,4-dione derivatives are:



Compound	R1	R2	Formula
314088	Br	Me	C ₁₇ H ₁₄ BrCl ₂ N ₃ O ₂
314089	OPr	Me	C ₂₀ H ₂₁ Cl ₂ N ₃ O ₃
314090	OEt	Me	C ₁₉ H ₁₉ Cl ₂ N ₃ O ₃
314091	OCF ₃	Me	C ₁₈ H ₁₄ Cl ₂ F ₃ N ₃ O ₃
314092	OCF ₃	H	C ₁₇ H ₁₂ Cl ₂ F ₃ N ₃ O ₃
314093	CN	H	C ₁₇ H ₁₂ Cl ₂ N ₄ O ₂

SOURCE – Tanabe Seiyaku.

REFERENCES

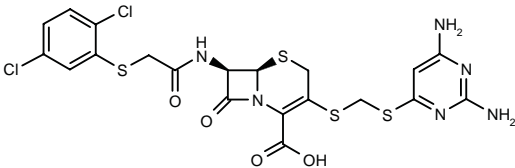
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ANTIINFECTIVE THERAPY

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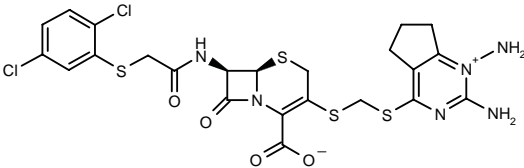
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314885: C23 H22 Cl2 N6 O4 S4

SOURCE – LG Chem.

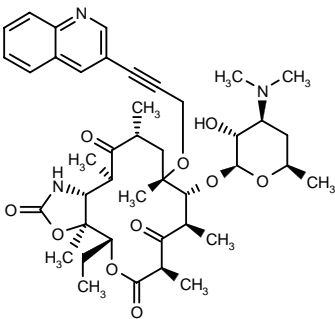
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A-217213

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SOURCE – Abbott.

REFERENCES

1. Or, Y.S. et al. (Abbott Laboratories Inc.) *6-*O*-Substd. ketolides having antibacterial activity*. EP 0929563, JP 2001500855, US 5866549, WO 9809978.

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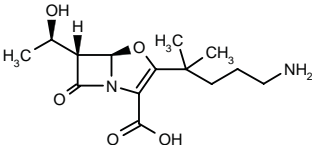
3. Nilius, A.M. et al. *In vitro and in vivo activities of A-217213, a new ketolide antibiotic, against respiratory tract pathogens*. 6th Int Conf Macrolides Azalides Streptogramins Ketolides Oxazolidinones (Jan 23-25, Bologna) 2002, Abst 1.05.

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AM-112^{2-7,9-11}

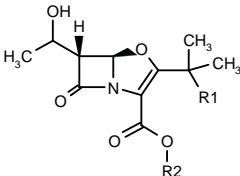
312527

(5*R*,6*R*)-2-(4-Amino-1,1-dimethylbutyl)-6-[1(*R*)-hydroxyethyl]-1-oxa-2-penem-3-carboxylic acid



C14 H22 N2 O5; Mol wt: 298.3368

ACTION – Oxapenem antibiotic with broad-spectrum activity against class A, class C and class D β-lactamases, giving IC₅₀ values ranging from < 0.0001 mg/l to 0.64 mg/l, versus values for clavulanic acid of 0.0016-92 mg/l. Compound was shown to reduce the MICs of cefazolin, cefaclor, ceftriaxone, cefoperazone, cefotaxime, ceftazidime, cefuroxime and cefepime against organisms producing both class A and class C β-lactamases. The synergistic activity of AM-112 in combination with ceftazidime against enterococci and *Escherichia coli* appeared to be mainly correlated with its ability to bind to and inhibit penicillin-binding proteins (PBPs). Compound also exhibited marked antibacterial activity against Gram-positive and anaerobic species including *Staphylococcus aureus* and *Streptococcus pneumoniae* (MIC = 1 and 0.5 µg/ml, respectively) and *Bacteroides* spp. (MIC = 2 µg/ml) In animal models of infection caused by β-lactamase-producing pathogens, compound was effective alone (ED₅₀ = 2.6 mg/kg s.c. against systemic infections caused by *S. aureus*) and also reduced the ED₅₀ of ceftazidime from 200 to 2 mg/kg s.c. against infections caused by *E. coli* carrying extended-spectrum class A β-lactamase, and from > 100 to 2 mg/kg against *Enterobacter cloacae* carrying class C β-lactamase. Pharmacokinetic studies in rats and mice showed that compound has similar pharmacokinetics to ceftazidime after i.v. administration but was poorly absorbed after oral administration; coadministration of ceftazidime (2:1) did not significantly affect AM-112 pharmacokinetics. Other related compounds are:



Compound	R1	R2	Isomer	Formula
AM-113 [312528] ^{4,7,8}	Me	K	R	C ₁₂ H ₁₆ KNO ₅
AM-114 [312529] ^{1,4,7}	Me	K	S	C ₁₂ H ₁₆ KNO ₅
AM-115 [312530] ^{1,4,7}	(CH ₂) ₃ NH ₂	H	S	C ₁₄ H ₂₂ N ₂ O ₅

SOURCE – Amura.

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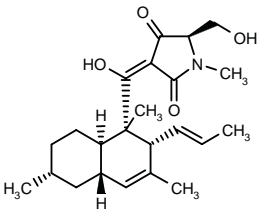
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CJ-21,058

315330

5(*R*)-(Hydroxymethyl)-3(*E*)-[1-hydroxy-1-[(1*S*,2*R*,4*aS*,6*R*,8*aR*)-1,3,6-trimethyl-2-[1(*E*)-propenyl]-1,2,4*a*,5,6,7,8,8*a*-octahydronaphthalen-1-yl]methylene]-1-methylpyrrolidine-2,4-dione

5'-Epiequisetin



C23 H33 N O4; Mol wt: 387.5167

ACTION – Antibacterial agent isolated from the fermentation broth of an unidentified fungus CL47745, with antibacterial activity against multidrug-resistant *Staphylococcus aureus* and *Enterococcus faecalis* (MIC = 5 µg/ml). Compound was shown to inhibit SecA (IC₅₀ = 15 µg/ml), a dimer subunit of the complex multisubunit translocase preprotein, and its antibacterial activity appeared to be mediated by inhibition of ATP-dependent translocation of preproteins across the bacterial cell membrane.

SOURCE – Pfizer.

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ERTAPENEM SODIUM

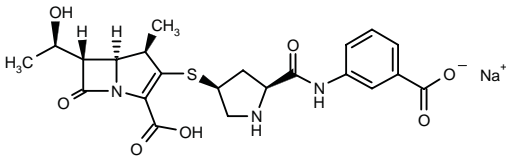
Prop INNM, USAN

236885

(1*R*,5*S*,6*S*)-2-[2(*S*)-[*N*-(3-Carboxyphenyl)carbamoyl]-pyrrolidin-4(*S*)-ylsulfanyl]-6-[1(*R*)-hydroxyethyl]-1-methyl-1-carba-2-penem-3-carboxylic acid monosodium salt

(4*R*,5*S*,6*S*)-3-[2(*S*)-[*N*-(3-Carboxyphenyl)carbamoyl]-pyrrolidin-4(*S*)-ylsulfanyl]-6-[1(*R*)-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-en-2-carboxylic acid monosodium salt

L-749345+
MK-0826
MK-826
ZD-4433+



C22 H24 N3 Na O7 S; Mol wt: 497.5016

ACTION – Parenteral carbapenem antibiotic.

INDICATION – Treatment of moderate to severe infections in adults caused by many common Gram-positive and Gram-negative aerobic and anaerobic bacteria.

PRESENTATION – Sterile lyophilized powder in single-dose vials, 1.046 g ertapenem sodium equivalent to 1 g ertapenem for i.v. or i.m. injection.

PROPRIETARY NAME – *Invanz* (US).

SOURCES – Merck & Co.; licensed from AstraZeneca.

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49. *FDA clears injectable antibiotic Invanz*. DailyDrugNews.com (Daily Essentials) 2001, Dec 3.

50. *Merck & Co. outlines new cycle of breakthrough medicines at San Francisco conference*. DailyDrugNews.com (Daily Essentials) 2002, Jan 17.

51. *Merck cites strong growth in presentation to analysts. Momentum of key products fuels confidence in company's future*. Merck & Co., Inc. Press Release 2000, Dec 12

52. *MK-0826 development status*. Merck & Co., Inc. Company Communication 2000, June 30.

53. *U.S. launch of new injectable carbapenem announced by Merck*. DailyDrugNews.com (Daily Essentials) 2002, March 1.

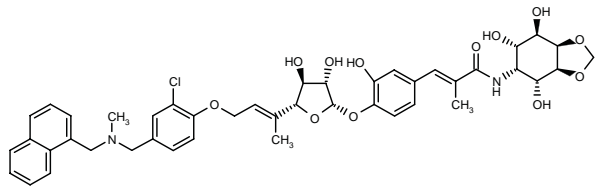
MONOGRAPH – Sorbera, L.A. et al. *MK-0826*. Drugs Fut 2000, 25(8): 0795.

*Drug Data Rep 1996, 018(11): 0997.

ANTIBACTERIAL DRUGS

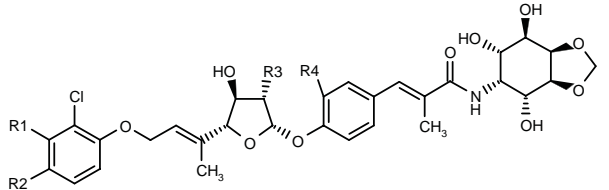
314004

3-[4-[7-O-[2-Chloro-4-[N-methyl-N-(naphthalen-1-yl-methyl)aminomethyl]phenyl]-5,6-dideoxy-5-methyl- β -D-arabino-5(E)-heptenofuranosyloxy]-3-hydroxyphenyl]-2-methyl-N-[(3a S, 4 R, 5 R, 6 S, 7 R, 7a R)-4,6,7-trihydroxyperhydro-1,3-benzodioxol-5-yl]-2(E)-propenamide



C44 H49 Cl N2 O12; Mol wt: 833.3261

ACTION – Hygromycin A derivative with potential for the treatment of bacterial and protozoal infections. Other specifically claimed compounds include the following:



Compound	R1	R2	R3	R4	Formula
314005	H	CH2N(CH2Ph)-CH2CH2N(Me)2	H	OH	C ₄₃ H ₅₄ ClN ₃ O ₁₁
314008	H	3-Cl-PhCH2NHCH2	OH	OH	C ₃₉ H ₄₄ Cl ₂ N ₂ O ₁₂
314010	1-Pip	H	OH	OH	C ₃₆ H ₄₅ ClN ₂ O ₁₂
314013	H	CH2N(Me)CH2Ph	OH	OH	C ₄₀ H ₄₇ ClN ₂ O ₁₂
314015	H	CH2N(Me)Et	OH	OH	C ₃₅ H ₄₅ ClN ₂ O ₁₂
314017	H	3-Cl-PhCH2NHCH2	OH	H	C ₃₉ H ₄₄ Cl ₂ N ₂ O ₁₁

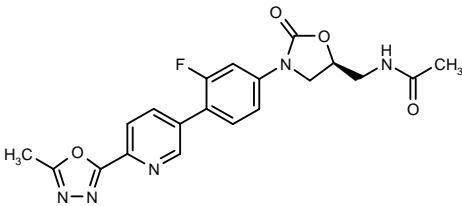
SOURCE – Pfizer.

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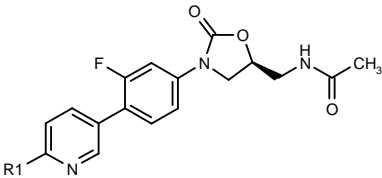
314261

N-[3-[3-Fluoro-4-[6-(5-methyl-1,3,4-oxadiazol-2-yl)pyridin-3-yl]phenyl]-2-oxooxazolidin-5(S)-ylmethyl]acetamide



C20 H18 F N5 O4; Mol wt: 411.3912

ACTION – Oxazolidinone antibacterial agent with potent activity against a broad spectrum of bacteria. For example, it exhibited MIC₅₀ values of 0.39, 0.2 and 3.13 µg/ml, respectively, against methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant enterococci and *Haemophilus influenzae*, and of 0.1 µg/ml against *Mycobacterium tuberculosis* ATCC 35837 and ATCC 27294. Other exemplified compounds are:



Compound	R1	Formula
314262	1,2,4-triazol-1-yl	C ₁₉ H ₁₆ FN ₅ O ₄
314263	1-tetrazolyl	C ₁₈ H ₁₆ FN ₇ O ₃
314264	5-Me-1,2,4-oxadiazol-3-yl	C ₂₀ H ₁₈ FN ₅ O ₄
314265	1-Me-5-tetrazolyl	C ₁₉ H ₁₈ FN ₇ O ₃
314267	2-Me-5-tetrazolyl	C ₁₉ H ₁₈ FN ₇ O ₃
314268	2-oxo-3-oxazolidinyl	C ₂₀ H ₁₉ FN ₄ O ₅

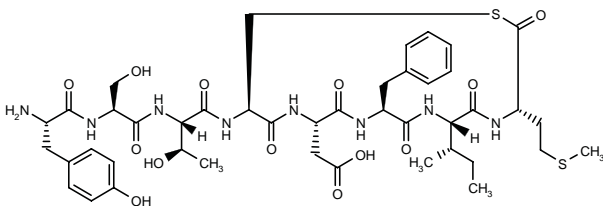
SOURCE – Dong-A.

REFERENCES

1. Lee, J.-G. et al. (Dong-A Pharmaceutical Co., Ltd.) *Novel oxazolidinone derivs. and a process for the preparation thereof*. WO 0194342.

314581

L-Tyrosyl-L-seryl-L-threonyl-L-cysteinyl-L-α-aspartyl-L-phenylalanyl-L-isoleucyl-L-methionine C-1.8-S-3.4-thiolactone



C43 H60 N8 O13 S2; Mol wt: 961.1220

ACTION – Cyclic peptide useful for the treatment of *Staphylococcus aureus* infections, reported to interfere with the Agr autoinduction system of *S. aureus*, thus preventing proliferation. It was able to inhibit the proliferation of *S. aureus* strains SA502A and RN8463 with IC₅₀ values of 2.9 and 3.2 nM, respectively, while displaying no Agr pathway-activating activity.

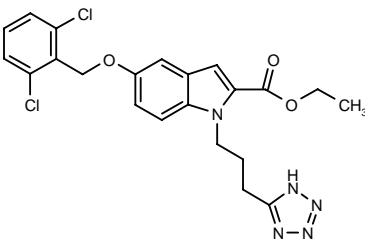
SOURCES – New York University, New York, NY (US); Rockefeller University, New York, NY (US).

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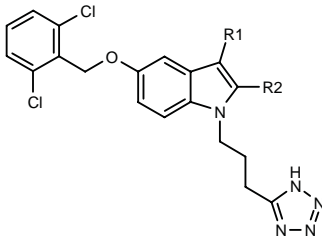
314920

5-(2,6-Dichlorobenzyloxy)-1-[3-(1*H*-tetrazol-5-yl)propyl]-1*H*-indole-2-carboxylic acid ethyl ester



C22 H21 Cl2 N5 O3; Mol wt: 474.3459

ACTION – Antibacterial agent that acts as a fatty acid synthase FabH inhibitor and is considered to have potential in the treatment of Gram-positive and Gram-negative bacterial infections. Other specifically claimed compounds are:



Compound	R1	R2	Formula
314921	H	4-morpholinyl-CO	C ₂₄ H ₂₄ Cl ₂ N ₆ O ₃
314922	H	i-BuNHCO	C ₂₄ H ₂₆ Cl ₂ N ₆ O ₂
314923	H	CON(Et)2	C ₂₄ H ₂₆ Cl ₂ N ₆ O ₂
314924	CHO	CO2Et	C ₂₃ H ₂₁ Cl ₂ N ₅ O ₄
314925	H	3-Me-1,2,4-oxadiazol-5-yl	C ₂₂ H ₁₈ Cl ₂ N ₇ O ₂
314926	H	H	C ₁₉ H ₁₇ Cl ₂ N ₅ O
314927	COEt	H	C ₂₂ H ₂₁ Cl ₂ N ₅ O ₂
314928	H	CH=NOMe	C ₂₁ H ₂₀ Cl ₂ N ₆ O ₂
314929	H	5-oxazolyl	C ₂₂ H ₁₈ Cl ₂ N ₆ O ₂

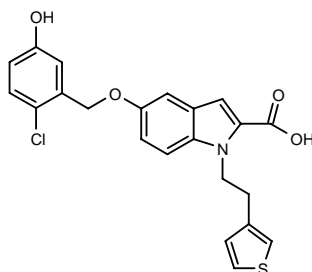
SOURCE – GlaxoSmithKline.

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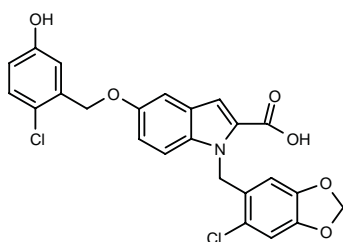
314930

5-(2-Chloro-5-hydroxybenzyloxy)-1-[2-(3-thienyl)ethyl]-1*H*-indole-2-carboxylic acid



C22 H18 Cl N O4 S; Mol wt: 427.9062

ACTION – Antibacterial agent that acts as a fatty acid synthase FabH inhibitor and is considered to have potential in the treatment of Gram-positive and Gram-negative bacterial infections. Another specifically claimed compound is:



314931: C24 H17 Cl2 N O6

SOURCE – GlaxoSmithKline.

REFERENCES

1. Daines, R.A. et al. (GlaxoSmithKline Inc.) *Fatty acid synthase inhibitors*. WO 0200620.

ANTI-PcrV MAb

315087

Humanized monoclonal antibody against PcrV, an antigen in Pseudomonas aeruginosa type III secretion system

ACTION – Humanized monoclonal antibody against *Pseudomonas aeruginosa* V antigen. The murine antibody was able to protect mice against pneumonia induced by *P. aeruginosa* PA103.

SOURCES – InterMune; Medical College of Wisconsin, Milwaukee, WI (US); Protein Design Labs.

REFERENCES

1. Frank, D.W. et al. (MCW Research Foundation, Inc.) *Method of and compsns. for immunization with the Pseudomonas V antigen*. WO 0033872.

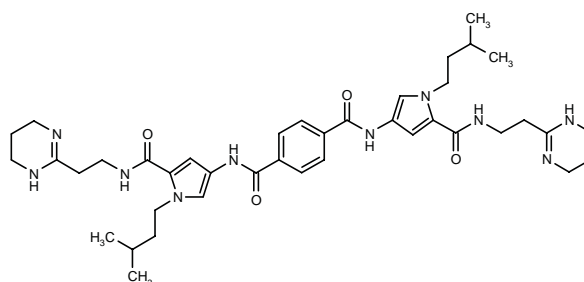
2. *InterMune to develop compound for the treatment and prevention of Pseudomonas infection*. InterMune Press Release 2001, Aug 16.

3. *Protein Design Labs and InterMune announced antibody humanization agreement*. InterMune Press Release 2000, Nov 28.

GL-757899¹⁻³

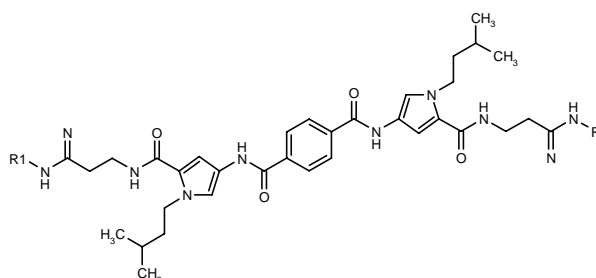
312940

N,N'-Bis[1-(3-methylbutyl)-5-[*N*-[2-(1,4,5,6-tetrahydropyrimidin-2-yl)ethyl]carbamoyl]-1*H*-pyrrol-3-yl]-benzene-1,4-dicarboxamide



C40 H56 N10 O4; Mol wt: 740.9484

ACTION – Antibacterial agent, a minor groove DNA binder with a strong stabilizing effect on DNA duplex formation and potent activity against vancomycin-resistant enterococci and methicillin-resistant *Staphylococcus aureus* (MIC = 0.7 µM). Other related compounds are:



Compound	R1	Formula
GL-898298 [312939] ¹⁻³	H	C ₃₄ H ₄₈ N ₁₀ O ₄
314998 ^{1,3}	Me	C ₃₆ H ₅₂ N ₁₀ O ₄
GL-179101 [315000] ¹⁻³	Et	C ₃₈ H ₅₆ N ₁₀ O ₄

SOURCE – Genelabs.

REFERENCES

1. Zhang, W. et al. (Genelabs Technologies, Inc.) *Novel cpds. possessing antibacterial, antifungal or antitumor activity*. WO 0200650.

2. Dyatkina, N. et al. *A new family of DNA targeting compounds are bacteriostatic for vancomycin resistant enterococci and methicillin resistant Staphylococcus aureus*. 41st Intersci Conf Antimicrob Agents Chemother (Dec 16-19, Chicago) 2001, Abst F-1699.

3. Dyatkina, N.B. et al. *Minor groove DNA binders as antimicrobial agents. 1. Pyrrole tetraamides are potent antibacterials against vancomycin resistant enterococci and methicillin resistant Staphylococcus aureus*. J Med Chem 2002, 45(4): 805.

INH-A21

315375

Human IgG monoclonal antibody against staphylococcal fibrinogen-binding proteins SdrG and ClfA

INH-A00021

ACTION – Human monoclonal antibody directed against staphylococcal fibrinogen-binding proteins, proven to prevent the induction of experimental *Staphylococcus epidermidis* endocarditis in rabbits (40% at 200 mg/kg i.v.) and to attenuate disease severity compared to control animals.

SOURCES – Inhibitex; Nabi.

REFERENCES

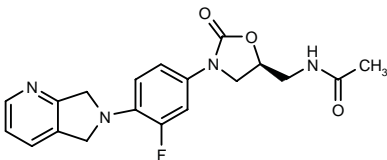
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2. Kupperwasser, L.I. et al. *Prevention of experimental Staphylococcus epidermidis (SE) endocarditis (IE) by passive immunotherapy with INH-A00021, a human IgG directed against staphylococcal fibrinogen-binding proteins*. 41st Intersci Conf Antimicrob Agents Chemother (Dec 16-19, Chicago) 2001, Abst G-1715.

RWJ-337813

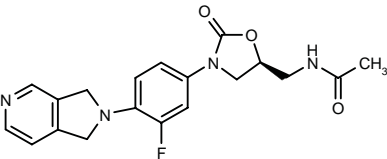
306399

N-[3-[4-(6,7-Dihydro-5H-pyrrolo[3,4-b]pyridin-6-yl)-3-fluorophenyl]-2-oxooxazolidin-5(S)-ylmethyl]acetamide



C19 H19 F N4 O3; Mol wt: 370.3821

ACTION – Oxazolidinone antibacterial agent, with improved *in vitro* antimicrobial activity against multidrug-resistant Gram-positive bacteria compared to linezolid. Compound was active against staphylococci including methicillin-resistant *Staphylococcus aureus* (MRSA; MIC = 0.25-2 µg/ml), enterococci including vancomycin-resistant strains (MIC = 0.25-0.5 µg/ml) and pneumococci (MIC = 0.25 µg/ml), and it was also active against *Haemophilus influenzae* (MIC = 8 µg/ml). *In vivo*, it proved effective against systemic murine infections caused by *S. aureus* Smith (ED₅₀ = 10 and 11 mg/kg/day s.c. and p.o., respectively), with activity comparable to linezolid; in a model of lower respiratory tract infection caused by *Streptococcus pneumoniae*, compound was more effective than linezolid (ED₅₀ = 11 and 20 mg/kg/day s.c., respectively, and 10 and 14 mg/kg/day p.o., respectively). It was also active in a pouch model with methicillin-sensitive or -resistant *S. aureus*. Another related compound is:



RWJ-334181 [306401]: C19 H19 F N4 O3

SOURCE – R.W. Johnson.

REFERENCES

1. Paget, S. and Hlasta, D. (Ortho-McNeil Pharmaceutical, Inc.) *Antibacterial heterobicyclic substd. phenyl oxazolidinones*. WO 0142242.

2. Foleno, B.D. et al. *In vitro antibacterial activity of the pyrrolopyridine-substituted oxazolidinones RWJ-334181 and RWJ-337813*. 41st Intersci Conf Antimicrob Agents Chemother (Dec 16-19, Chicago) 2001, Abst F-1049.

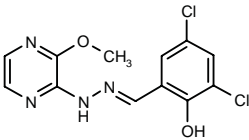
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4. Paget, S. et al. *Synthesis and antibacterial activity of pyrrolopyridine-substituted oxazolidinones*. 41st Intersci Conf Antimicrob Agents Chemother (Dec 16-19, Chicago) 2001, Abst F-1048.

ANTIFUNGAL AGENTS

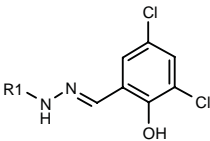
313633

3,5-Dichloro-2-hydroxybenzaldehyde (3-methoxypyrazin-2-yl)hydrazone



C12 H10 Cl2 N4 O2; Mol wt: 313.1430

ACTION – Antifungal hydrazone that displayed MIC values of 1, 1 and 2 µg/ml, respectively, against *Candida albicans*, *Saccharomyces cerevisiae* and *Aspergillus nidulans*. Other exemplified compounds are:



Compound	R1	Formula
313634	3-Cl-2-pyrazinyl	C ₁₁ H ₇ Cl ₃ N ₄ O
313635	3,5-(CF3)2-PhNHCS	C ₁₆ H ₅ Cl ₂ F ₆ N ₃ OS

SOURCE – Anadys Pharmaceuticals.

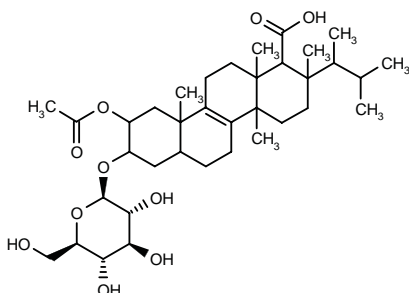
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EM-F2300A

315145

9-Acetoxy-2-(1,2-dimethylpropyl)-8-(β -D-glucopyranosyloxy)-2,4a,10a,12a-tetramethyl-1,2,3,4,4a,5,6,6a,7,8,9,10,10a,11,12,12a-hexadecahydrochrysene-1-carboxylic acid



C36 H58 O10; Mol wt: 650.8442

ACTION – Antifungal agent isolated from cultures of *Humicola* sp. Mer-f2300 (FERM P-17589), shown to inhibit the adhesion of *Candida albicans* to IEC-18 cells. Compound gave MIC values of 0.78, 6.25 and 25 μ g/ml, respectively, against *Saccharomyces cerevisiae* G2-10, *Aspergillus fumigatus* Tsukuba and *Staphylococcus aureus* ATCC 29213.

SOURCES – Eisai; Mercian.

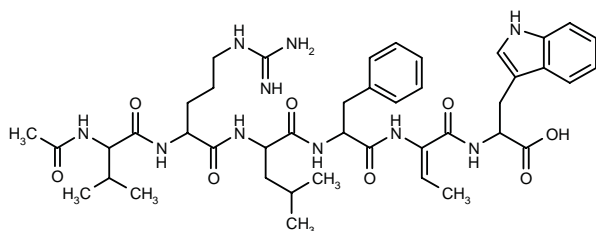
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EM-F2368

315147

N-Acetyl-DL-valyl-DL-arginyl-DL-leucyl-DL-phenylalanyl-2-amino-2-butenoyl-DL-tryptophan



C43 H60 N10 O8; Mol wt: 845.0090

ACTION – Peptide compound with fungal adhesion-inhibitory activity, as demonstrated using *Candida albicans* and IEC-18 cells, isolated from cultures of *Mortierella alpina* Mer-f2368 (FERM P-17653).

SOURCES – Eisai; Mercian.

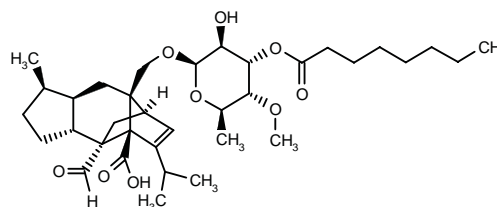
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GM-160575¹⁻⁴

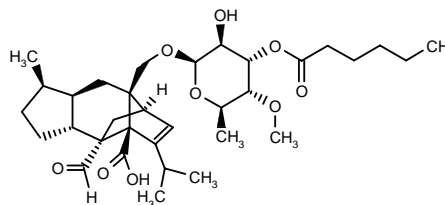
314226

(1*R*,3*aR*,4*S*,4*aR*,7*R*,7*aR*,8*aS*)-8a-(6-Deoxy-4-*O*-methyl-3-*O*-octanoyl- β -D-altropyranosyloxymethyl)-4-formyl-3-isopropyl-7-methyl-1,3*a*,4,4*a*,5,6,7,7*a*,8,8*a*-decahydro-1,4-methano-*s*-indacene-3*a*-carboxylic acid



C35 H54 O9; Mol wt: 618.8026

ACTION – Antifungal agent, a sordarin derivative with strong activity against *Candida albicans* (MIC < 0.001-0.06 μ g/ml), *Candida pseudotropicalis*, *Candida tropicalis* and *Cryptococcus neoformans* (MIC = 0.004, 0.06 and 0.25 μ g/ml, respectively). Another related compound is:



314227^{1,2}: C33 H50 O9

SOURCE – GlaxoSmithKline.

REFERENCES

1. Hayes, M. et al. (GlaxoSmithKline plc) *Antifungal sordarin derivs*. EP 0711783, EP 0791007, JP 1999502188, US 6054478, WO 9614327.
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4. Domínguez, J.M. et al. *Sordarins: A new class of antifungals with selective inhibition of the protein synthesis elongation cycle in yeasts*. Antimicrob Agents Chemother 1998, 42(9): 2274.

MYCOGRAB

315336

Recombinant human antibody against heat shock protein 90 (hsp90)

ACTION – Human recombinant antibody against the heat shock protein 90 (hsp90) complex of *Candida albicans*, with a wide spectrum of activity against pathogenic yeasts and synergistic activity with amphotericin B both *in vitro* and in murine candidiasis. Results from a clinical study in 4 patients with disseminated candidiasis showed that the antibody was well tolerated, did not induce changes in laboratory parameters and showed favorable pharmacokinetics. At the dose of 1 mg/kg/day, the antibody produced clinical improvement in all patients treated.

SOURCES – University of Manchester, Manchester (GB); NeuTec Pharma.

REFERENCES

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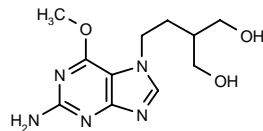
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3. *Antibody therapy to fight deadly bugs*. University of Manchester Press Release 2000, Oct 15.

ANTIVIRAL DRUGS

314240

2-[2-(2-Amino-6-methoxy-7*H*-purin-7-yl)ethyl]propane-1,3-diol



C11 H17 N5 O3; Mol wt: 267.2873

ACTION – A purine derivative with antiviral activity, particularly useful against herpesvirus, flavivirus and hepadnavirus infections. The compound gave an EC₅₀ of 0.4 μM against hepatitis B virus in an *in vitro* assay.

SOURCE – CSIRO, Clayton (AU).

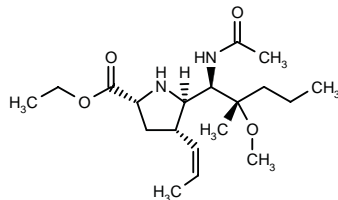
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A-315677^{1,3-5}

312460

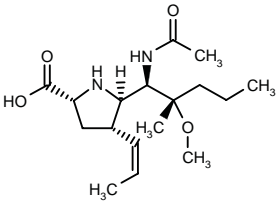
5(*R*)-[1(*R*)-Acetamido-2(*S*)-methoxy-2-methylpentyl]-4(*S*)-[1(*Z*)-propenyl] pyrrolidine-2(*R*)-carboxylic acid ethyl ester



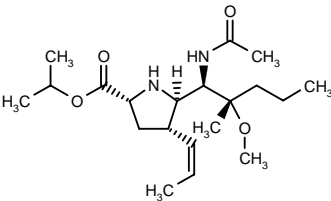
C19 H34 N2 O4; Mol wt: 354.4876

ACTION – Prodrug of **A-315675**, a potent inhibitor of influenza virus neuraminidase (K_i = 0.07-0.21 nM against influenza A enzyme; K_i = 0.14-0.31 nM against influenza B enzyme), with improved oral bioavailability. Pharmacokinetic studies in rats, dogs and cynomolgus monkeys showed a rapid increase in plasma levels of A-315675, with a peak within 1 h after administration of prodrug. The plasma levels of A-315675 measured after administration of the prodrug were 3-fold higher in dogs and > 60-fold higher in rats compared to the levels measured after A-315675. The prodrug provides about 2-fold

improvement in oral bioavailability in dogs. In a mouse model of influenza A and influenza B infection, compound demonstrated significant efficacy, with ED₅₀ values of 7.74 and 0.00383 mg/kg/day b.i.d for 3 days p.o., respectively. Another prodrug is **A-322278**.



A-315675^{*1-5} [304097]: C17 H30 N2 O4



A-322278^{1,3-5} [312971]: C20 H36 N2 O4

SOURCE – Abbott.

REFERENCES

1. Maring, C.J. et al. (Abbott Laboratories Inc.) *Inhibitors of neuraminidases*. WO 0128996.

2. Carrick, R.J. et al. *In vitro generation and characterization of an A/N9 influenza virus resistant to a novel neuraminidase (NA) inhibitor A-315675*. 41st Intersci Conf Antimicrob Agents Chemother (Dec 16-19, Chicago) 2001, Abst H-1582.

3. Kempf-Grote, A. et al. *The contributions of prodrug modification of the pharmacokinetic profile A-315675, a potent neuraminidase inhibitor*. 41st Intersci Conf Antimicrob Agents Chemother (Dec 16-19, Chicago) 2001, Abst A-503.

4. Raja, S.N. et al. *Radiosynthesis and rat tissue distribution studies of novel neuraminidases inhibitors*. 41st Intersci Conf Antimicrob Agents Chemother (Dec 16-19, Chicago) 2001, Abst F-1683.

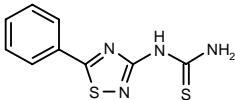
5. Zielinski Mozny, N.A. et al. *Biological efficacy of pro-drugs of A-315675 compared to GS4104 against B Hong Kong (B/HK/5/72) and Tokyo (A/N2/Tokyo/3/67) influenza in a BALB/c murine model*. 41st Intersci Conf Antimicrob Agents Chemother (Dec 16-19, Chicago) 2001, Abst H-1583.

*Identified compound **304097** Drug Data Rep 2001, 023(09): 0901.

COMPOUND 301029

315011

N-(5-Phenyl-1,2,4-thiadiazol-3-yl)thiourea



C9 H8 N4 S2; Mol wt: 236.3222

ACTION – Antiviral agent active against bovine viral diarrhea virus (BVDV); it acts by inhibiting intermediate steps in the virus replication cycle, resulting in a significant reduction in RNA synthesis. Compound also showed antiviral activity against hepatitis C virus (HCV). Pharmacokinetic studies in mice showed a moderately rapid decline from the systemic circulation, with an elimination half-life of 413 min; the low oral bioavailability needs to be improved by formulation strategies.

SOURCE – Procter & Gamble.

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1. Agyin, J.K. (The Procter & Gamble Co.) *Process for the preparation of 1,2,4-thiadiazoles*. US 6297384.

2. Camden, J.B. (The Procter & Gamble Co.) *Thiadiazolyl urea or thiourea derivs. for antiviral treatment*. US 6258831, WO 0057878.

3. Camden, J.B. (The Procter & Gamble Co.) *Viral treatment*. US 6245788, WO 0057869.

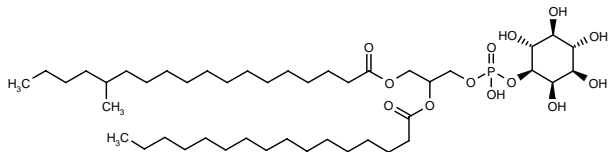
4. Camden, J.B. (The Procter & Gamble Co.) *Viral treatment*. US 6340696.

5. Wong, H. et al. *Liquid chromatography-mass spectrometry assay of a thiadiazole derivative in mice: Application to pharmacokinetic studies*. J Chromatogr B - Biomed Sci Appl 2001, 765(1): 55.

S-420B-A

314407

14-Methyloctadecanoic acid 2-(hexadecanoyloxy)-3-[(hydroxy)[2(*R*),3(*R*),4,5(*S*),6(*R*)-pentahydroxycyclohexyloxy]phosphoryloxy]propyl ester



C44 H85 O13 P; Mol wt: 853.1165

ACTION – Phospholipid isolated from a culture of *Rhodococcus equi* S420 strain (FERM P-17817) with *in vitro* activity against influenza A virus strains A/PR/8/34, Singapore/1/57 and Aichi/2/68.

SOURCE – Mercian.

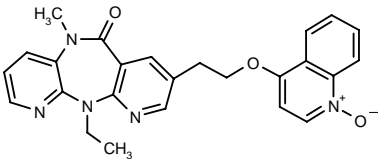
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AIDS MEDICINES

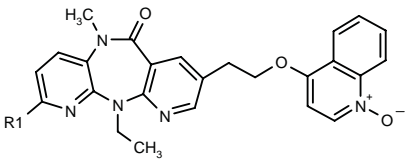
314520

11-Ethyl-5-methyl-8-[2-(1-oxidoquinolin-4-yloxy)ethyl]-6,11-dihydro-5*H*-dipyrido[2,3-*e*:3',2'-*b*][1,4]diazepin-6-one



C25 H23 N5 O3; Mol wt: 441.4887

ACTION – Non-nucleoside reverse transcriptase inhibitor shown to inhibit the enzyme from a panel of HIV strains with IC₅₀ values in the nanomolar range and to inhibit the proliferation of wild-type and mutant HIV strains. Other specifically claimed dipyrido[2,3-*e*:3',2'-*b*][1,4]diazepine derivatives are:



Compound	R1	Formula
314521	Cl	C ₂₅ H ₂₂ ClN ₅ O ₃
314522	F	C ₂₅ H ₂₂ FN ₅ O ₃

SOURCE – Boehringer Ingelheim.

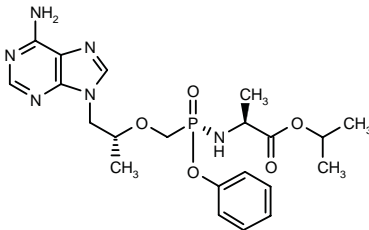
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1. Simoneau, B. (Boehringer Ingelheim [Canada] Ltd.) *Non-nucleoside reverse transcriptase inhibitors*. WO 0196338.

GS-7340

315936

N-[[(*S_P*)-[2-(Adenin-9-yl)-1(*R*)-methylethoxymethyl]-(phenoxy)phosphoryl]-L-alanine isopropyl ester



C21 H29 N6 O5 P; Mol wt: 476.4711

ACTION – Oral prodrug of tenofovir that is stable in plasma and is selectively metabolized to tenofovir and the mono- and diphosphates in peripheral blood mononuclear cells (PBMCs). In dogs and monkeys administered a single oral dose of compound, the oral bioavailability of tenofovir was about 20%; the concentration of tenofovir in PBMCs was increased by > 38-fold compared with tenofovir disoproxil. *In vitro*, it was at least 5-fold more potent than tenofovir disoproxil and at least 500-fold more potent than tenofovir against HIV (EC₅₀ = 5 nM), and it also potently inhibited hepatitis B virus (HBV) replication (EC₅₀ = 10 nM).

SOURCE – Gilead.

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1. Becker, M.W. et al. (Gilead Sciences Inc.) *Prodrugs of phosphonate nucleotide analogues and methods for selecting and making same*. WO 0208241.

2. Chapman, H. et al. *Practical synthesis, separation, and stereochemical assignment of the PMPA prodrug GS-7340*. Nucleosides Nucleotides Nucleic Acids 2001, 20(4-7): 621.

3. Chapman, H. et al. *Purification of PMPA amide prodrugs by SMB chromatography and x-ray crystallography of the diastereomerically pure GS-7340*. Nucleosides Nucleotides Nucleic Acids 2001, 20(4-7): 1085.

4. Eisenberg, E.J. et al. *Metabolism of GS-7340, a novel phenyl monophosphoramidate intracellular prodrug of PMPA, in blood*. Nucleosides Nucleotides Nucleic Acids 2001, 20(4-7): 1091.

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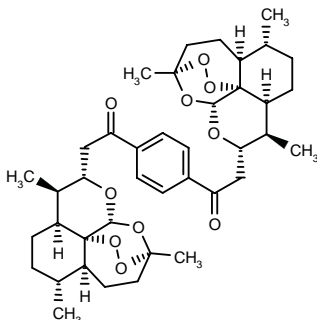
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7. Lynch, T. et al. *LC/MS determination of the intracellular concentration of two novel aryl phosphoramidate prodrugs of PMPA and their metabolites in dog PBMC*. Nucleosides Nucleotides Nucleic Acids 2001, 20(4-7): 1415.

TREATMENT OF PROTOZOAL DISEASES

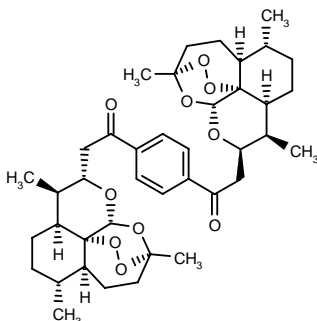
314345

1,1'-(1,4-Phenylene)bis[2-[(3*R*,5*aS*,6*R*,8*aS*,9*R*,10*S*,12*R*,12*aR*)-3,6,9-trimethyl-3,12-epoxyperhydropyrano[4,3-*J*]-1,2-benzodioxepin-10-yl]ethanone]



C40 H54 O10; Mol wt: 694.8566

ACTION – Artemisinin derivative with *in vitro* antiprotozoal activity against chloroquine-sensitive *Plasmodium falciparum* (IC₅₀ = 3.9 nM) and growth-inhibitory activity against the NCI panel of 60 human cancer cell lines. Potentially useful for the treatment of malaria and cancer. Another related compound is:



314344: C40 H54 O10

SOURCE – Johns Hopkins University, Baltimore, MD (US).

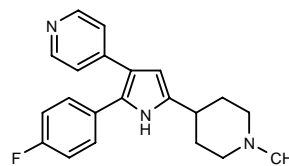
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1. Posner, G.H. et al. (Hauser, Inc.; Johns Hopkins University) *C-10 carbon-substd. artemisinin-like trioxane cpds. having antimalarial, antiproliferative and antitumour activities*. EP 1043988, JP 2001527043, US 6156790, US 6160004, WO 9933461.

2. Posner, G.H. et al. *New chemical and biological aspects of artemisinin-derived trioxane dimers*. Bioorg Med Chem 2002, 10(1): 227.

315280

4-[2-(4-Fluorophenyl)-5-(1-methylpiperidin-4-yl)-1*H*-pyrrol-3-yl]pyridine



C21 H22 F N3; Mol wt: 335.4238

ACTION – Selective inhibitor of protozoan cGMP-dependent protein kinase proven to inhibit the intracellular replication of *Toxoplasma gondii* tachyzoites with IC₅₀ values of 210-230 nM. A dose of 50 mg/kg i.p. b.i.d. for 10 days completely protected mice from *T. gondii* infection and no evidence of clinical recrudescence was seen for up to 12 months. Five days after cessation of treatment parasites could be detected in spleen, brain and lungs, indicating asymptomatic recrudescence in these animals, but parasite load peak decreased within the first 5-10 days after cessation of treatment and reached undetectable levels 50 days after inoculation. Immunocompetent mice cured by treatment with compound were able to survive rechallenge with a lethal dose of *T. gondii*. Together with data from interferon gamma knockout mice, these results indicate that the efficacy of compound against *T. gondii* depends upon a functional immune system.

SOURCE – Merck & Co.

REFERENCES

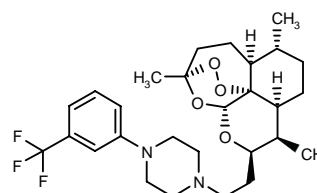
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2. Nare, B. et al. *Evaluation of a cyclic GMP-dependent protein kinase inhibitor in treatment of murine toxoplasmosis: Gamma interferon is required for efficacy*. Antimicrob Agents Chemother 2002, 46(2): 300.

315960

1-[3-(Trifluoromethyl)phenyl]-4-[2-[(3*R*,5*aS*,6*R*,8*aS*,9*R*,10*S*,12*R*,12*aR*)-3,6,9-trimethylperhydro-3,12-epoxypyrano[4,3-*J*]-1,2-benzodioxepin-10-yl]ethyl]-piperazine

10(*R*)-[2-[4-[3-(Trifluoromethyl)phenyl]piperazin-1-yl]ethyl]-10-deoxyartemisinin



C28 H39 F3 N2 O4; Mol wt: 524.6201

ACTION – Antimalarial agent, an artemisinin derivative with an IC₅₀ value of 6.19 nM against *Plasmodium falciparum* *in vitro* and an ED₅₀ value of 3.12 mg/kg *in vivo* in *Plasmodium berghei*-infected mice. Compound exhibited improved water solubility, metabolic stability and *in vivo* efficacy compared with sodium artesunate.

SOURCE – University of Liverpool, Liverpool (GB).

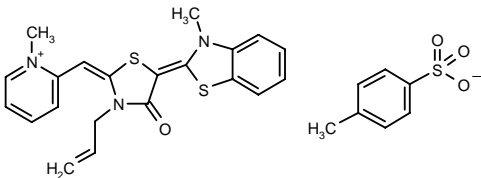
REFERENCES

1. Hindley, S. et al. *Mechanism-based design of parasite-targeted artemisinin derivatives: Synthesis and antimalarial activity of new diamine containing analogues.* J Med Chem 2002, 45(5): 1052.

MKH-57

315938

2-[3-Allyl-5-(3-methyl-2,3-dihydrobenzothiazol-2-ylidene)-4-oxothiazolidin-2-ylidenemethyl]-1-methylpyridinium 4-methylbenzenesulfonate



C21 H20 N3 O S2 . C7 H7 O3 S; Mol wt: 565.7363

ACTION – Antimalarial agent, a rhodacyanine dye with an EC₅₀ value of 12 nM against a chloroquine-sensitive strain of *Plasmodium falciparum* and low cytotoxicity against murine mammary tumor FM3A cells (EC₅₀ = 12 μM).

SOURCE – Fujii Photo Film.

REFERENCES

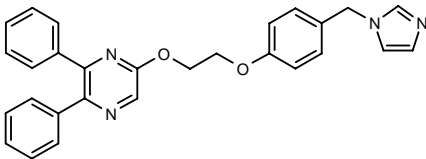
1. Takasu, K. et al. *Rhodacyanine dyes as antimalarials. 1. Preliminary evaluation of their activity and toxicity.* J Med Chem 2002, 45(5): 995.

TREATMENT OF MUSCULOSKELETAL AND CONNECTIVE TISSUE DISEASES

ANTIARTHRITIC DRUGS

311269

5-[2-[4-(1*H*-Imidazol-1-ylmethyl)phenoxy]ethoxy]-2,3-diphenylpyrazine



C28 H24 N4 O2; Mol wt: 448.5236

ACTION – Antiinflammatory agent, an inhibitor of nitric oxide (NO) production with an IC₅₀ value of 0.27 μM against lipopolysaccharide/interferon gamma-induced NO production in RAW 264.7 cells. *In vivo*, compound exhibited antiinflammatory activity in two models of arthritis in mice, affording significant protection at 10 and 30 mg/kg/day p.o. against adjuvant- and collagen-induced arthritis, respectively.

SOURCE – SSP.

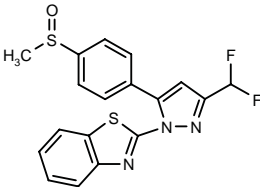
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1. Konno, F. et al. (SSP Co., Ltd.) *Imidazole derivs. or salts thereof and drugs containing the derivs. or the salts.* WO 0200648.

2. Konno, F. et al. *Novel anti-inflammatory agents with NO (nitric oxide) inhibition.* 21st Symp Med Chem (Nov 28-30, Kyoto) 2001, Abst 2P-24.

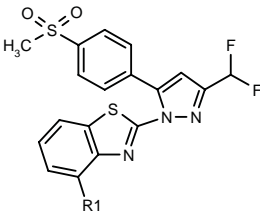
313550

2-[3-(Difluoromethyl)-5-[4-(methylsulfinyl)phenyl]-1*H*-pyrazol-1-yl]benzothiazole



C18 H13 F2 N3 O S2; Mol wt: 389.4487

ACTION – Selective cyclooxygenase type 2 (COX-2) inhibitor with IC₅₀ values of 0.94 and 19 μM, respectively, against COX-2 and COX-1 (20-fold selectivity). *In vivo*, it displayed antiinflammatory and antinociceptive activity in a rat model of adjuvant-induced arthritis following oral administration. Moreover, no deaths or significant changes in body weight were observed in acute toxicity tests in mice administered 300 mg/kg p.o. Potentially useful as an antiinflammatory agent devoid of gastric side effects. Other exemplified pyrazole-substituted benzothiazole derivatives include the following:



Compound	R1	Formula
313551	H	C ₁₈ H ₁₃ F ₂ N ₃ O ₂ S ₂
313552	F	C ₁₈ H ₁₂ F ₃ N ₃ O ₂ S ₂

SOURCE – Grelan.

REFERENCES

1. Aotsuka, T. et al. (Grelan Pharmaceutical Co., Ltd.) *1-(Benzothiazol-2-yl)pyrazole derivs. and COX-2 inhibitors containing the same.* WO 0187880.

SOURCE – University of Liverpool, Liverpool (GB).

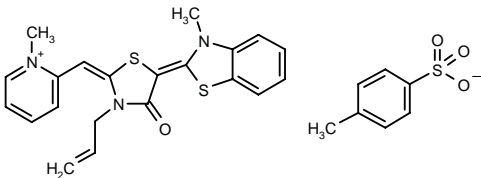
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1. Hindley, S. et al. *Mechanism-based design of parasite-targeted artemisinin derivatives: Synthesis and antimalarial activity of new diamine containing analogues.* J Med Chem 2002, 45(5): 1052.

MKH-57

315938

2-[3-Allyl-5-(3-methyl-2,3-dihydrobenzothiazol-2-ylidene)-4-oxothiazolidin-2-ylidenemethyl]-1-methylpyridinium 4-methylbenzenesulfonate



C21 H20 N3 O S2 . C7 H7 O3 S; Mol wt: 565.7363

ACTION – Antimalarial agent, a rhodacyanine dye with an EC₅₀ value of 12 nM against a chloroquine-sensitive strain of *Plasmodium falciparum* and low cytotoxicity against murine mammary tumor FM3A cells (EC₅₀ = 12 μM).

SOURCE – Fujii Photo Film.

REFERENCES

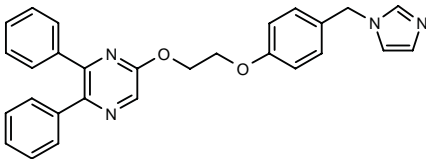
1. Takasu, K. et al. *Rhodacyanine dyes as antimalarials. 1. Preliminary evaluation of their activity and toxicity.* J Med Chem 2002, 45(5): 995.

TREATMENT OF MUSCULOSKELETAL AND CONNECTIVE TISSUE DISEASES

ANTIARTHRITIC DRUGS

311269

5-[2-[4-(1*H*-Imidazol-1-ylmethyl)phenoxy]ethoxy]-2,3-diphenylpyrazine



C28 H24 N4 O2; Mol wt: 448.5236

ACTION – Antiinflammatory agent, an inhibitor of nitric oxide (NO) production with an IC₅₀ value of 0.27 μM against lipopolysaccharide/interferon gamma-induced NO production in RAW 264.7 cells. *In vivo*, compound exhibited antiinflammatory activity in two models of arthritis in mice, affording significant protection at 10 and 30 mg/kg/day p.o. against adjuvant- and collagen-induced arthritis, respectively.

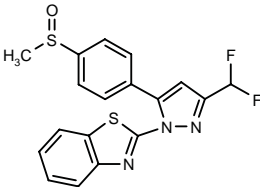
SOURCE – SSP.

REFERENCES

1. Konno, F. et al. (SSP Co., Ltd.) *Imidazole derivs. or salts thereof and drugs containing the derivs. or the salts.* WO 0200648.
2. Konno, F. et al. *Novel anti-inflammatory agents with NO (nitric oxide) inhibition.* 21st Symp Med Chem (Nov 28-30, Kyoto) 2001, Abst 2P-24.

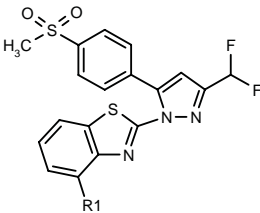
313550

2-[3-(Difluoromethyl)-5-[4-(methylsulfinyl)phenyl]-1*H*-pyrazol-1-yl]benzothiazole



C18 H13 F2 N3 O S2; Mol wt: 389.4487

ACTION – Selective cyclooxygenase type 2 (COX-2) inhibitor with IC₅₀ values of 0.94 and 19 μM, respectively, against COX-2 and COX-1 (20-fold selectivity). *In vivo*, it displayed antiinflammatory and antinociceptive activity in a rat model of adjuvant-induced arthritis following oral administration. Moreover, no deaths or significant changes in body weight were observed in acute toxicity tests in mice administered 300 mg/kg p.o. Potentially useful as an antiinflammatory agent devoid of gastric side effects. Other exemplified pyrazole-substituted benzothiazole derivatives include the following:



Compound	R1	Formula
313551	H	C ₁₈ H ₁₃ F ₂ N ₃ O ₂ S ₂
313552	F	C ₁₈ H ₁₂ F ₃ N ₃ O ₂ S ₂

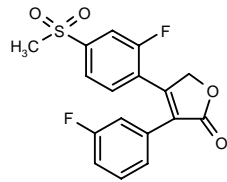
SOURCE – Grelan.

REFERENCES

1. Aotsuka, T. et al. (Grelan Pharmaceutical Co., Ltd.) *1-(Benzothiazol-2-yl)pyrazole derivs. and COX-2 inhibitors containing the same.* WO 0187880.

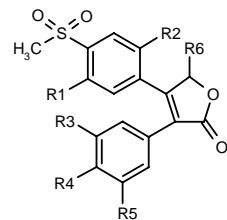
313822

4-[2-Fluoro-4-(methylsulfonyl)phenyl]-3-(3-fluorophenyl)-furan-2(5*H*)-one



C17 H12 F2 O4 S; Mol wt: 350.3398

ACTION – Selective cyclooxygenase type 2 (COX-2) inhibitor giving an IC₅₀ of 0.578 μM against COX-2 and showing > 2,000-fold selectivity over COX-1. *In vivo*, it was able to inhibit carrageenan-induced paw edema in rats following oral administration. Potentially useful in the treatment of a broad range of inflammatory conditions including arthritis, pain, fever, Alzheimer’s disease, dysmenorrhea, preterm labor, asthma, bronchitis, inflammatory bowel disease, gastritis, Crohn’s disease, ulcerative colitis, peptic ulcers, cancer, bacterial infections, dermatitis, psoriasis, allergic rhinitis, atherosclerosis, retinopathy, respiratory distress syndrome, etc. Other exemplified heterocyclic compounds are:



Compound	R1	R2	R3	R4	R5	R6	Formula
313824	Me	H	H	H	H	H	C ₁₈ H ₁₆ O ₄ S
313826	F	H	Me	SMe	H	H	C ₁₉ H ₁₇ F ₄ O ₄ S ₂
313827	Me	H	Me	OMe	H	H	C ₂₀ H ₂₀ O ₅ S
313828	H	F	Me	OMe	H	H	C ₁₉ H ₁₇ FO ₅ S
313829	F	H	H	F	H	Et	C ₁₉ H ₁₆ F ₂ O ₄ S
313830	H	F	F	F	H	H	C ₁₇ H ₁₁ F ₃ O ₄ S
313831	H	F	F	H	F	H	C ₁₇ H ₁₁ F ₃ O ₄ S
313832	F	H	Me	SMe	H	Et	C ₂₁ H ₂₁ FO ₄ S ₂
313833	F	H	H	F	H	Me	C ₁₈ H ₁₄ F ₂ O ₄ S

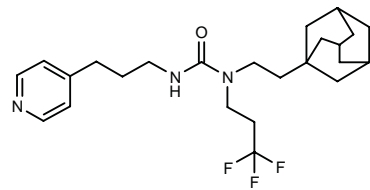
SOURCE – Dr. Reddy’s Research Foundation.

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1. Pal, M. et al. (Dr. Reddy’s Research Foundation) *Novel cpds. having antiinflammatory activity: Process for their preparation and pharmaceutical compsns. containing them.* WO 0190097.

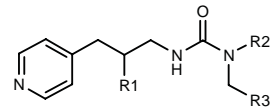
314070

N-[2-(1-Adamantyl)ethyl]-*N*’-[3-(4-pyridyl)propyl]-*N*-(3,3,3-trifluoropropyl)urea



C24 H34 F3 N3 O; Mol wt: 437.5466

ACTION – TNF-α production inhibitor proven to reduce lipopolysaccharide (LPS)-induced production of TNF-α by 95.8% following oral administration to rats at 10 mg/kg. Potentially useful for the treatment of chronic rheumatoid arthritis, Crohn’s disease, autoimmune diseases such as systemic lupus erythematosus, cachexia, acute infection, allergy, fever, anemia, diabetes, etc. Other exemplified compounds are:



Compound	R1	R2	R3	Formula
314071	H	t-BuOCON(Me)CH2CH2	1-adamantyl-CH2	C ₂₉ H ₄₆ N ₄ O ₃
314072	H	C5H11	1-adamantyl-CH2	C ₂₆ H ₄₁ N ₃ O
314073	H	CH2CH=C(Me)2	1-adamantyl-CH2	C ₂₆ H ₃₉ N ₃ O
314074	H	CH2Ph	Ph	C ₂₃ H ₂₅ N ₃ O
314075	H	C5H11	cyclohexyl-CH2	C ₂₂ H ₃₇ N ₃ O
314076	Me	C5H11	1-adamantyl-CH2	C ₂₇ H ₄₃ N ₃ O
314077	Me	t-BuOCON(Me)CH2CH2	1-adamantyl-CH2	C ₃₀ H ₄₈ N ₄ O ₃

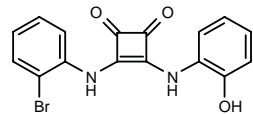
SOURCE – Santen.

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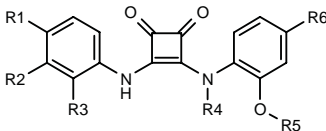
314110

3-(2-Bromophenylamino)-4-(2-hydroxyphenylamino)-3-cyclobutene-1,2-dione



C16 H11 Br N2 O3; Mol wt: 359.1779

ACTION – Chemokine IL-8 (CXCR1, CXCR2) receptor antagonist, potentially useful for the treatment of arthritis, atopic dermatitis, asthma, chronic obstructive pulmonary disease, adult respiratory distress syndrome, inflammatory bowel disease, Crohn’s disease, ulcerative colitis, stroke, septic shock, multiple sclerosis, psoriasis, cardiac and renal reperfusion injury, thrombosis, transplant rejection, Alzheimer’s disease, malaria, restenosis, atherosclerosis, osteoporosis and angiogenesis, among other IL-8-mediated conditions. Other related compounds are:



Compound	R1	R2	R3	R4	R5	R6	Formula
314111	H	H	Br	H	H	CN	C ₁₇ H ₁₀ BrN ₃ O ₃
314112	H	H	OH	H	Me	H	C ₁₇ H ₁₄ N ₂ O ₄
314113	CN	H	OH	H	H	CN	C ₁₈ H ₁₀ N ₄ O ₄
314114	H	OMe	OMe	H	H	H	C ₁₈ H ₁₆ N ₂ O ₅
314115	H	H	H	Me	H	H	C ₁₇ H ₁₄ N ₂ O ₃

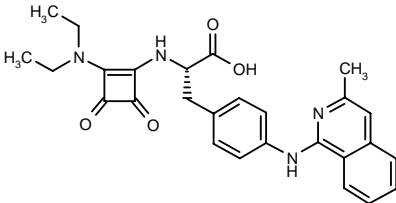
SOURCE – GlaxoSmithKline.

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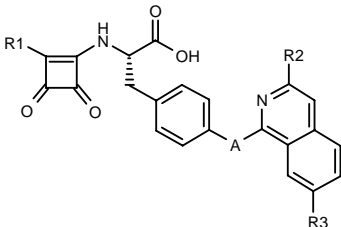
314153

N-[2-(Diethylamino)-3,4-dioxo-1-cyclobuten-1-yl]-4-(3-methylisoquinolin-1-ylamino)-L-phenylalanine



C27 H28 N4 O4; Mol wt: 472.5422

ACTION – Potent and selective inhibitor of α_4 integrins such as $\alpha_4\beta_1$ and $\alpha_4\beta_7$. By virtue of its ability to modulate cell adhesion, this compound is expected to be useful for the treatment of inflammatory and immune disorders including arthritis, vasculitis, polydermatomyositis, multiple sclerosis, transplant rejection, diabetes, psoriasis, dermatitis, asthma and inflammatory bowel disease. Other exemplified 3-substituted isoquinoline-containing squaric acid derivatives are:



Compound	R1	R2	R3	A	Formula
314154	cis-2,5-(Me)2-1-pyrrolidinyl	Me	Cl	NH	C ₂₉ H ₂₉ ClN ₄ O ₄
314155	N(Et)2	Me	F	NH	C ₂₇ H ₂₇ FN ₄ O ₄
314156	N(Et)2	Me	OMe	NH	C ₂₈ H ₃₀ N ₄ O ₅
314157	N(Pr)2	Cl	H	O	C ₂₈ H ₂₈ ClN ₃ O ₅
314158	trans-2,5-(Me)2-1-pyrrolidinyl	Cl	H	O	C ₂₈ H ₂₆ ClN ₃ O ₅
314159	hexahydro-1-azepinyl	Cl	H	O	C ₂₈ H ₂₆ ClN ₃ O ₅

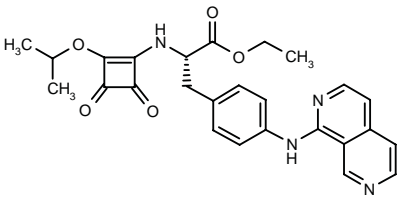
SOURCE – Celltech Group.

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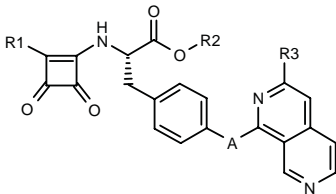
314161

N-(2-Isopropoxy-3,4-dioxo-1-cyclobuten-1-yl)-4-(2,7-naphthyridin-1-ylamino)-L-phenylalanine ethyl ester



C26 H26 N4 O5; Mol wt: 474.5144

ACTION – Potent and selective inhibitor of α_4 integrins such as $\alpha_4\beta_1$ and $\alpha_4\beta_7$. By virtue of its ability to modulate cell adhesion, this compound is expected to be useful for the treatment of inflammatory and immune disorders including arthritis, vasculitis, polydermatomyo-sitis, multiple sclerosis, transplant rejection, diabetes, psoriasis, dermatitis, asthma and inflammatory bowel disease. Other exemplified 2,7-naphthyridine-containing squaric acid derivatives are:



Compound	R1	R2	R3	A	Formula
314162	1-pyrrolidinyl	H	H	NH	C ₂₅ H ₂₃ N ₅ O ₄
314163	OEt	Et	H	O	C ₂₅ H ₂₃ N ₅ O ₆
314164	hexahydro-1-azepinyl	H	Me	NH	C ₂₈ H ₂₉ N ₅ O ₄
314165	cis-2,5-(Me)2-1-pyrrolidinyl	H	Et	NH	C ₂₉ H ₃₁ N ₅ O ₄
314166	hexahydro-1-azepinyl	Et	Me	NH	C ₃₀ H ₃₃ N ₅ O ₄
314167	3,5-(Me)2-1-Pip	H	H	NH	C ₂₈ H ₂₉ N ₅ O ₄
314168	4-(t-BuOCO)-perhydro-1,4-diazepin-1-yl	H	H	NH	C ₃₁ H ₃₄ N ₆ O ₆
314169	N(Et)CH2Ph	H	Me	O	C ₃₁ H ₂₈ N ₄ O ₅

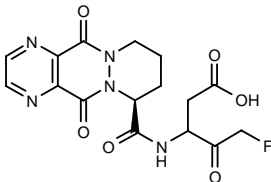
SOURCE – Celltech Group.

REFERENCES

1. Langham, B.J. et al. (Celltech Group plc) *2,7-Naphthyridine derivs*. WO 0192256.

314244

3-[5,12-Dioxo-5,7,8,9,10,12-hexahydropyrazino[2,3-d]pyridazino[1,2-a]pyridazin-7(S)-ylcarboxamido]-5-fluoro-4-oxopentanoic acid



C16 H16 F N5 O6; Mol wt: 393.3294

ACTION – Caspase inhibitor proven to inhibit Fas-induced apoptosis in Jurkat E6.1 cells with an IC₅₀ value of 168 nM, indicating its ability to inhibit caspase 8. Potentially useful for the treatment of a broad range of disorders mediated by apoptosis and inflammation such as autoimmune diseases, inflammatory diseases, destructive bone disorders, proliferative disorders, infections and alcohol abuse.

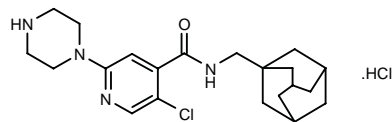
SOURCE – Vertex.

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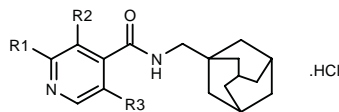
314325

N-(Adamantan-1-ylmethyl)-5-chloro-2-(1-piperazinyl)-pyridine-4-carboxamide hydrochloride



C21 H29 Cl N4 O . HCl; Mol wt: 425.4010

ACTION – A P2X₇ receptor antagonist with potential in the treatment of rheumatoid arthritis and chronic obstructive pulmonary disease, as well as psoriasis, allergic dermatitis, asthma, septic shock, glomerulonephritis, irritable bowel disease, Crohn’s disease, ulcerative colitis, atherosclerosis, cancer, diabetes, Alzheimer’s disease, meningitis, osteoporosis, burn injury, ischemic heart disease and stroke. Other specifically claimed adamantane derivatives are:



Compound	R1	R2	R3	Formula
314326	perhydro-1,4-diazepin-1-yl	H	Cl	C ₂₂ H ₃₁ ClN ₄ O.HCl
314327	4-NH2-1-Pip	H	Cl	C ₂₂ H ₃₁ ClN ₄ O.HCl
314328	4-Pip-CH2NH	H	Cl	C ₂₃ H ₃₃ ClN ₄ O.HCl
314329	3-NH2-1-pyrrolidinyl	H	Cl	C ₂₁ H ₂₉ ClN ₄ O.HCl
314331	4-Pip-O	H	Cl	C ₂₂ H ₃₀ ClN ₃ O ₂ .HCl
314333	4-Pip-CH2O	H	Cl	C ₂₃ H ₃₂ ClN ₃ O ₂ .HCl
314334	3-Pip-CH2O	H	Cl	C ₂₃ H ₃₂ ClN ₃ O ₂ .HCl
314336	4-NH2-1-Pip	Cl	H	C ₂₂ H ₃₁ ClN ₄ O.HCl
314337	4-Pip-CH2NH	Cl	H	C ₂₃ H ₃₃ ClN ₄ O.HCl

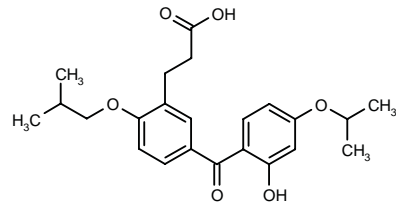
SOURCE – AstraZeneca.

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1. Alcaraz, L. and Furber, M. (AstraZeneca AB) *Adamantane derivs*. WO 0194338.

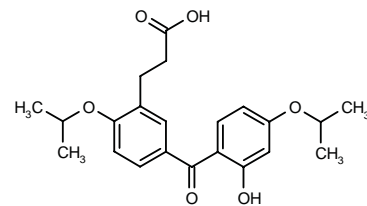
314409

3-[5-(2-Hydroxy-4-isopropoxybenzoyl)-2-isobutoxy-phenyl]propionic acid



C23 H28 O6; Mol wt: 400.4682

ACTION – Antiinflammatory agent for use in the treatment of arthritis, proven to inhibit arthritis and bone destruction by 73 and 84%, respectively, at 3 mg/kg/day p.o. for 15 days in mice with collagen-induced arthritis. Another exemplified benzophenone derivative is:



314410: C22 H26 O6

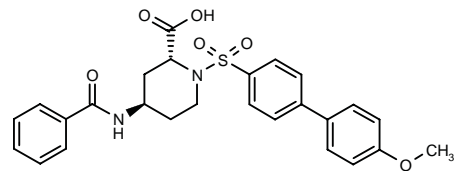
SOURCE – Toyama.

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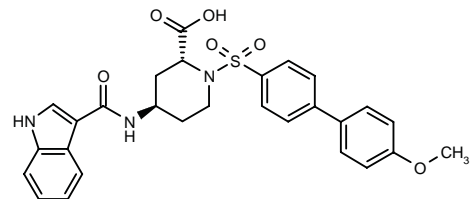
314591

4(R)-Benzamido-1-(4'-methoxybiphenyl-4-ylsulfonyl)-piperidine-2(R)-carboxylic acid



C26 H26 N2 O6 S; Mol wt: 494.5654

ACTION – Matrix metalloproteinase (MMP) inhibitor, potentially useful for the treatment of diseases associated with MMP-mediated destruction of extracellular matrix. Compound gave IC₅₀ values of 10 nM, 1.2 μM and 0.90 μM, respectively, against MMP-2 (gelatinase A), MMP-9 (gelatinase B) and membrane type 1 MMP (MMP-14). Another exemplified pipecolic acid derivative is:



314592: C28 H27 N3 O6 S

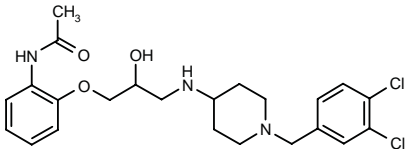
SOURCE – Kotobuki.

REFERENCES

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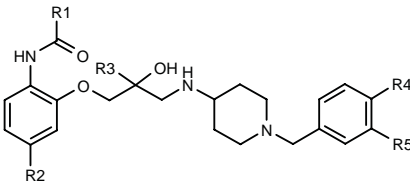
314684

N-[2-[3-[1-(3,4-Dichlorobenzyl)piperidin-4-ylamino]-2-hydroxypropoxy]phenyl]acetamide

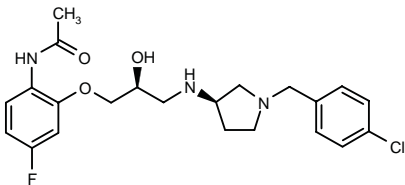


C23 H29 Cl2 N3 O3; Mol wt: 466.4061

ACTION – Chemokine receptor, particularly MIP-1α receptor, modulator, potentially useful for the treatment of immune, autoimmune, inflammatory and proliferative disorders including rheumatoid arthritis, chronic obstructive pulmonary disease, asthma and multiple sclerosis. Other specifically claimed compounds are:



Compound	R1	R2	R3	R4	R5	Formula
314685	Me	F	H	Cl	Cl	C ₂₃ H ₂₈ Cl ₂ FN ₃ O ₃
314686	i-Pr	H	H	Cl	H	C ₂₅ H ₃₄ ClN ₃ O ₃
314687	Me	F	H	Cl	H	C ₂₃ H ₂₉ ClFN ₃ O ₃
314688	Me	H	Me	Cl	H	C ₂₄ H ₃₂ ClN ₃ O ₃
314691	Ph	H	H	Br	H	C ₂₈ H ₃₂ BrN ₃ O ₃
314692	Me	OMe	H	Cl	H	C ₂₄ H ₃₂ ClN ₃ O ₄
314693	Me	H	Me	Br	H	C ₂₄ H ₃₂ BrN ₃ O ₃
314694	Me	H	H	F	H	C ₂₃ H ₃₀ FN ₃ O ₃



314689: C22 H27 Cl F N3 O3

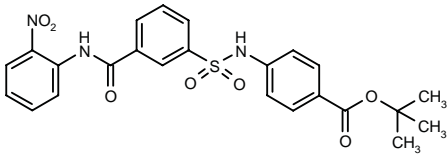
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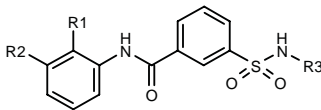
314699

4-[3-[N-(2-Nitrophenyl)carbamoyl]phenylsulfonamido]-benzoic acid *tert*-butyl ester



C24 H23 N3 O7 S; Mol wt: 497.5257

ACTION – Potent and selective phosphodiesterase type 7 (PDE7) inhibitor, potentially useful for the treatment of rheumatoid arthritis, multiple sclerosis, systemic lupus erythematosus, transplant rejection, psoriasis, post-angioplasty restenosis, atherosclerosis, osteoporosis, asthma, inflammatory bowel disease, pancreatitis, chronic obstructive pulmonary disease, chronic bronchitis, atopic dermatitis and allergic rhinitis. Other specifically claimed sulfonamide derivatives include the following:



Compound	R1	R2	R3	Formula
314700	CO ₂ H	H	2-Br-5-CF ₃ -Ph	C ₂₁ H ₁₄ BrF ₃ N ₂ O ₅ S
314701	CO ₂ H	H	4-Br-2-CF ₃ -Ph	C ₂₁ H ₁₄ BrF ₃ N ₂ O ₅ S
314702	CO ₂ H	H	4-Cl-1-Naph	C ₂₄ H ₁₇ ClN ₂ O ₅ S
314703	H	CO ₂ H	4-Cl-Ph	C ₂₀ H ₁₅ ClN ₂ O ₅ S
314705	CO ₂ H	H	4-Br-2-Et-Ph	C ₂₂ H ₁₉ BrN ₂ O ₅ S
314706	CO ₂ H	H	4-Cl-Ph	C ₂₀ H ₁₅ ClN ₂ O ₅ S
314707	CO ₂ H	H	4-CF ₃ -Ph	C ₂₁ H ₁₅ F ₃ N ₂ O ₅ S
314708	CO ₂ H	H	2-Me-5-CF ₃ -Ph	C ₂₂ H ₁₇ F ₃ N ₂ O ₅ S

SOURCE – Celltech Group.

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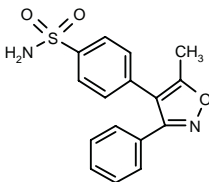
VALDECOXIB⁺

Prop INN, USAN

241522

4-(5-Methyl-3-phenylisoxazol-4-yl)benzenesulfonamide

SC-65872



C16 H14 N2 O3 S; Mol wt: 314.3660

ACTION – Antiinflammatory, analgesic and antipyretic agent, a selective cyclooxygenase type 2 (COX-2) inhibitor.

INDICATION – Treatment of the signs and symptoms of osteoarthritis and adult rheumatoid arthritis and treatment of pain associated with menstrual cramping.

PRESENTATION – Film-coated tablets, 10 and 20 mg.

PROPRIETARY NAME – Bextra (US).

SOURCES – Comarketed by Pfizer and Pharmacia.

RECENT REFERENCES

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4. Daniels, S.E. et al. *Pre-operative valdecoxib, a COX-2 specific inhibitor, provides effective and long-lasting pain relief following oral surgery.* Annu Meet Am Soc Anesthesiol (ASA) (Oct 13-17, New Orleans) 2001, Abst A-810.

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7. Goldstein, J.L. et al. *Comparative gastroduodenal mucosal effects of valdecoxib, a potent COX-2 specific inhibitor, compared with naproxen and placebo.* Gut 2001, 49(Suppl. 3): Abst 2166.

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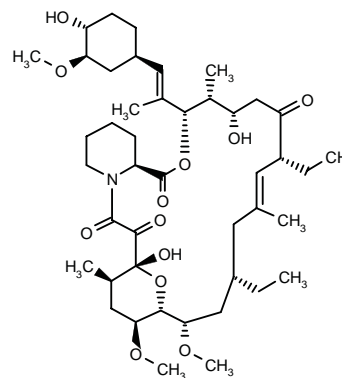
MONOGRAPH – Sorbera, L.A. et al. *Valdecoxib and Parecoxib Sodium.* Drugs Fut 2001, 26(2): 0133.

*Drug Data Rep 2000, 022(05): 0454.

IMMUNOMODULATING AGENTS

313777

(3*S*,4*R*,5*S*,8*R*,12*S*,14*S*,15*R*,16*S*,18*R*,19*R*,26*aS*)-8,12-Diethyl-5,19-dihydroxy-3-[(*E*)-2-[(1*R*,3*R*,4*R*)-4-hydroxy-3-methoxycyclohexyl]-1-methylvinyl]-14,16-dimethoxy-4,10,18-trimethyl-3,4,5,6,7,8,11,12,13,14,15,16,17,18,19,20,21,23,24,25,26,26*a*-docosahydro-1*H*-15,19-epoxypyrido[2,1-*c*][1,4]oxazacyclotricosine-1,7,20,21-tetraone



C44 H71 N O12; Mol wt: 806.0399

ACTION – Immunosuppressant for the treatment of inflammatory conditions, shown to inhibit the allergen-mediated stimulation of CD4⁺ antigen-specific human helper T-cells with an IC₅₀ of 0.33 nM. Potentially useful for the treatment of inflammatory and hyper-proliferative skin diseases such as psoriasis and dermatitis, allergic diseases including extrinsic asthma, rhinitis, conjunctivitis, atopic eczema, urticaria and food and drug allergy, and also for the treatment of graft rejection, arthritis, systemic lupus erythematosus, multiple sclerosis, type 1 diabetes, intestinal diseases and alopecia areata. Other exemplified macrolides are:

INDICATION – Treatment of the signs and symptoms of osteoarthritis and adult rheumatoid arthritis and treatment of pain associated with menstrual cramping.

PRESENTATION – Film-coated tablets, 10 and 20 mg.

PROPRIETARY NAME – Bextra (US).

SOURCES – Comarketed by Pfizer and Pharmacia.

RECENT REFERENCES

1. Agrawal, N. et al. *Supratherapeutic doses of valdecoxib have reduced incidence of gastroduodenal ulcers compared with conventional therapeutic doses of naproxen in osteoarthritis and rheumatoid arthritis patients.* Gut 2001, 49(Suppl. 3): Abst 2157.

2. Bensen, W. et al. *Valdecoxib, a new COX-2 specific inhibitor, is effective in treating the signs and symptoms of rheumatoid arthritis.* Arthritis Rheum 2001, 44(9, Suppl.): S369.

3. Camu, F. et al. *The COX-2 specific inhibitor valdecoxib is opioid-sparing and provides effective analgesia in primary hip arthroplasty patients.* Annu Meet Am Soc Anesthesiol (ASA) (Oct 13-17, New Orleans) 2001, Abst A-809.

4. Daniels, S.E. et al. *Pre-operative valdecoxib, a COX-2 specific inhibitor, provides effective and long-lasting pain relief following oral surgery.* Annu Meet Am Soc Anesthesiol (ASA) (Oct 13-17, New Orleans) 2001, Abst A-810.

5. DeJardins, P.J. et al. *Pre-operative administration of valdecoxib, a potent COX-2 specific inhibitor, provides effective post-operative analgesia.* Annu Meet Am Soc Anesthesiol (ASA) (Oct 13-17, New Orleans) 2001, Abst A-811.

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8. Goldstein, J.L. et al. *Reduced incidence of gastroduodenal ulcers with valdecoxib compared to ibuprofen and diclofenac in patients with osteoarthritis: A multicenter trial.* Dig Dis Week (May 20-23, Atlanta) 2001, Abst 3032.

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19. *Industry leader Pfizer expects growth driven by broad and deep pipeline.* DailyDrugNews.com (Daily Essentials) 2002, Jan 21.

20. *Major approval obtained by Pharmacia/Pfizer for new antiinflammatory/analgesic.* DailyDrugNews.com (Daily Essentials) 2001, Nov 20.

21. *Pfizer achieves important milestones during Q2 2001.* DailyDrugNews.com (Daily Essentials) 2001, July 23.

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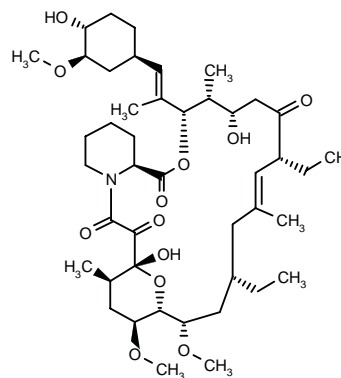
MONOGRAPH – Sorbera, L.A. et al. *Valdecoxib and Parecoxib Sodium.* Drugs Fut 2001, 26(2): 0133.

*Drug Data Rep 2000, 022(05): 0454.

IMMUNOMODULATING AGENTS

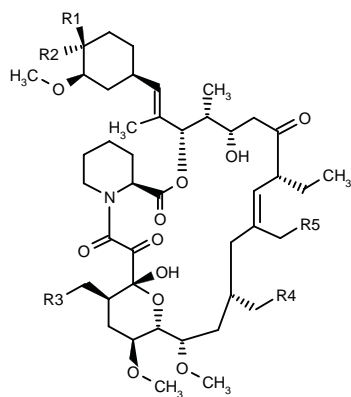
313777

(3*S*,4*R*,5*S*,8*R*,12*S*,14*S*,15*R*,16*S*,18*R*,19*R*,26*aS*)-8,12-Diethyl-5,19-dihydroxy-3-[(*E*)-2-[(1*R*,3*R*,4*R*)-4-hydroxy-3-methoxycyclohexyl]-1-methylvinyl]-14,16-dimethoxy-4,10,18-trimethyl-3,4,5,6,7,8,11,12,13,14,15,16,17,18,19,20,21,23,24,25,26,26*a*-docosahydro-1*H*-15,19-epoxypyrido[2,1-*c*][1,4]oxazacyclotricosine-1,7,20,21-tetraone



C44 H71 N O12; Mol wt: 806.0399

ACTION – Immunosuppressant for the treatment of inflammatory conditions, shown to inhibit the allergen-mediated stimulation of CD4⁺ antigen-specific human helper T-cells with an IC₅₀ of 0.33 nM. Potentially useful for the treatment of inflammatory and hyper-proliferative skin diseases such as psoriasis and dermatitis, allergic diseases including extrinsic asthma, rhinitis, conjunctivitis, atopic eczema, urticaria and food and drug allergy, and also for the treatment of graft rejection, arthritis, systemic lupus erythematosus, multiple sclerosis, type 1 diabetes, intestinal diseases and alopecia areata. Other exemplified macrolides are:



Compound	R1	R2	R3	R4	R5	Formula
313778	H	OH	Me	H	H	C ₄₄ H ₇₁ NO ₁₂
313781	Cl	H	H	H	Me	C ₄₄ H ₇₀ ClNO ₁₁
313782	Cl	H	H	Me	H	C ₄₄ H ₇₀ ClNO ₁₁
313783	Cl	H	Me	H	H	C ₄₄ H ₇₀ ClNO ₁₁

SOURCE – Novartis.

REFERENCES

1. Fleissner, G. et al. (Novartis AG;Novartis-Erfindungen VmbH) *Macrolides*. WO 0190110.

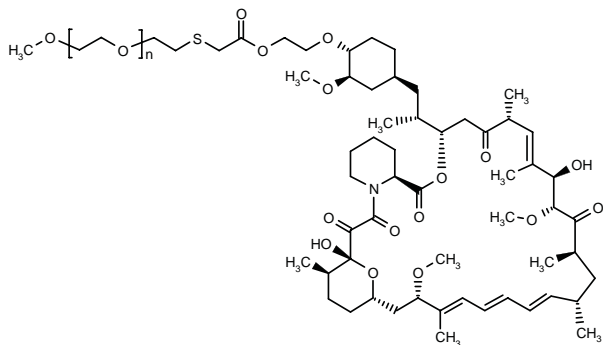
314497

(3*S*,6*R*,7*E*,9*R*,10*R*,12*R*,14*S*,15*E*,17*E*,19*E*,21*S*,23*S*,26*R*,27*R*,34*aS*)-9,27-Dihydroxy-10,21-dimethoxy-3-[2-[(1*S*,3*R*,4*R*)-3-methoxy-4-[2-[2-(monomethoxypolyethyleneglycol)ethylsulfanyl]acetoxy]ethoxy]cyclohexyl]-1(*R*)-methylethyl]-6,8,12,14,20,26-hexamethyl-3,4,5,6,9,10,11,12,13,14,21,22,23,24,25,26,27,28,29,31,32,33,34,34*a*-tetracosahydro-1*H*-23,27-epoxypyrido[2,1-*c*][1,4]oxaazacyclohentriacontine-1,5,11,28,29-pentaone

40-*O*-[2-[2-[2-(Monomethoxypolyethyleneglycol)ethylsulfanyl]-acetoxy]ethyl]rapamycin

[1*R*,9*S*,12*S*[1'*R*(1''*S*,3''*R*,4''*R*)],15*R*,18*R*,19*R*,21*R*,23*S*,30*S*,32*S*,35*R*]-1,18-Dihydroxy-19,30-dimethoxy-12-[2-[3-methoxy-4-[2-[2-[2-(monomethoxypolyethyleneglycol)ethylsulfanyl]acetoxy]ethoxy]cyclohexyl]-1-methylethyl]-15,17,21,23,29,35-hexamethyl-11,36-dioxo-4-azatricyclo[30.3.1.0^{4,9}]hexatriaconta-16(*E*),24(*E*),26(*E*),28(*E*)-tetraene-2,3,10,14,20-pentaone

SDZ-RAD–PEG 5000 conjugate



C58 H91 N O16 S(C2 H4 O)*n*; Mol wt: 1134.4670

ACTION – A soluble pegylated rapamycin (sirolimus) derivative shown to inhibit [³H]-thymidine incorporation into human glioblastoma U-87 MG cells. Potentially useful for the treatment of transplant rejection, fungal infections, rheumatoid arthritis, restenosis, pulmonary inflammation and glioblastoma.

SOURCE – Wyeth Pharmaceuticals.

REFERENCES

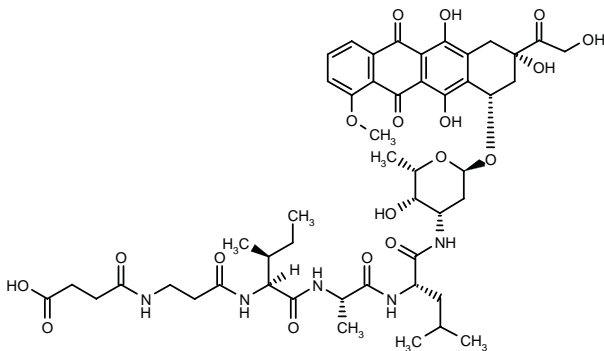
1. Zhu, T. et al. (American Home Products Corp.) *Water soluble SDZ RAD esters*. US 6331547.

ONCOLYTIC DRUGS

ANTIBIOTICS AND ALKALOIDS

314613

N-[*N*-(4-Hydroxysuccinyl)-β-alanyl-L-isoleucyl-L-alanyl-L-leucyl]doxorubicin



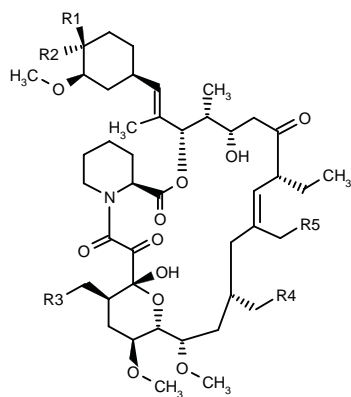
C49 H65 N5 O18; Mol wt: 1012.0700

ACTION – An isoleucine-containing peptide prodrug of the antitumor agent doxorubicin with an improved therapeutic index with respect to the free antitumor compound. This prodrug gave IC₅₀ values of 0.19, 57 and 38 μM, respectively, against the prostate cancer cell lines LNCaP and PC-3 and the colon adenocarcinoma cell line HT-29. It showed a maximum tolerated dose (MTD) approximately 10-fold higher than doxorubicin in acute toxicity tests in healthy mice, and 6.5-fold higher in tumor-bearing mice. The prodrug demonstrated rapid blood clearance and was mainly excreted in urine. Finally, compound proved effective *in vivo* in a mouse xenograft model of doxorubicin-resistant colorectal carcinoma LS 174T following i.v. administration.

SOURCE – Corixa.

REFERENCES

1. Pickford, L.B. et al. (Corixa Corp.) *Prodrug cpds. with isoleucine*. WO 0195943.



Compound	R1	R2	R3	R4	R5	Formula
313778	H	OH	Me	H	H	C ₄₄ H ₇₁ NO ₁₂
313781	Cl	H	H	H	Me	C ₄₄ H ₇₀ ClNO ₁₁
313782	Cl	H	H	Me	H	C ₄₄ H ₇₀ ClNO ₁₁
313783	Cl	H	Me	H	H	C ₄₄ H ₇₀ ClNO ₁₁

SOURCE – Novartis.

REFERENCES

1. Fleissner, G. et al. (Novartis AG;Novartis-Erfindungen VmbH) *Macrolides*. WO 0190110.

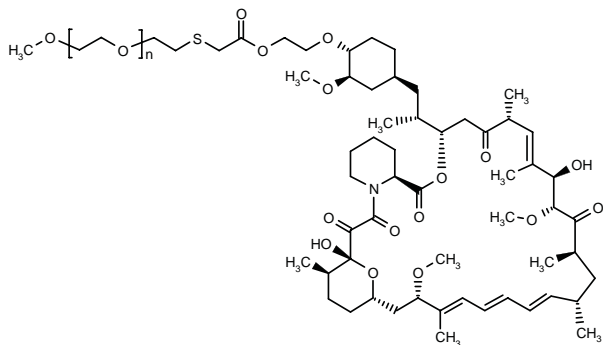
314497

(3*S*,6*R*,7*E*,9*R*,10*R*,12*R*,14*S*,15*E*,17*E*,19*E*,21*S*,23*S*,26*R*,27*R*,34*aS*)-9,27-Dihydroxy-10,21-dimethoxy-3-[2-[(1*S*,3*R*,4*R*)-3-methoxy-4-[2-[2-(monomethoxypolyethyleneglycol)ethylsulfanyl]acetoxylethoxy]cyclohexyl]-1(*R*)-methylethyl]-6,8,12,14,20,26-hexamethyl-3,4,5,6,9,10,11,12,13,14,21,22,23,24,25,26,27,28,29,31,32,33,34,34*a*-tetracosahydro-1*H*-23,27-epoxypyrido[2,1-*c*][1,4]oxaazacyclohentriacontine-1,5,11,28,29-pentaone

40-*O*-[2-[2-[2-(Monomethoxypolyethyleneglycol)ethylsulfanyl]-acetoxylethyl]rapamycin

[1*R*,9*S*,12*S*[1'*R*(1''*S*,3''*R*,4''*R*)],15*R*,18*R*,19*R*,21*R*,23*S*,30*S*,32*S*,35*R*]-1,18-Dihydroxy-19,30-dimethoxy-12-[2-[3-methoxy-4-[2-[2-[2-(monomethoxypolyethyleneglycol)ethylsulfanyl]acetoxylethoxy]cyclohexyl]-1-methylethyl]-15,17,21,23,29,35-hexamethyl-11,36-dioxo-4-azatricyclo[30.3.1.0^{4,9}]hexatriaconta-16(*E*),24(*E*),26(*E*),28(*E*)-tetraene-2,3,10,14,20-pentaone

SDZ-RAD-PEG 5000 conjugate



C58 H91 N O16 S(C2 H4 O)*n*; Mol wt: 1134.4670

ACTION – A soluble pegylated rapamycin (sirolimus) derivative shown to inhibit [³H]-thymidine incorporation into human glioblastoma U-87 MG cells. Potentially useful for the treatment of transplant rejection, fungal infections, rheumatoid arthritis, restenosis, pulmonary inflammation and glioblastoma.

SOURCE – Wyeth Pharmaceuticals.

REFERENCES

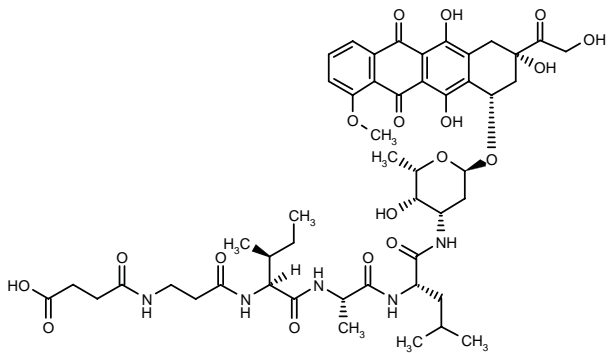
1. Zhu, T. et al. (American Home Products Corp.) *Water soluble SDZ RAD esters*. US 6331547.

ONCOLYTIC DRUGS

ANTIBIOTICS AND ALKALOIDS

314613

N-[*N*-(4-Hydroxysuccinyl)-β-alanyl-L-isoleucyl-L-alanyl-L-leucyl]doxorubicin



C49 H65 N5 O18; Mol wt: 1012.0700

ACTION – An isoleucine-containing peptide prodrug of the antitumor agent doxorubicin with an improved therapeutic index with respect to the free antitumor compound. This prodrug gave IC₅₀ values of 0.19, 57 and 38 μM, respectively, against the prostate cancer cell lines LNCaP and PC-3 and the colon adenocarcinoma cell line HT-29. It showed a maximum tolerated dose (MTD) approximately 10-fold higher than doxorubicin in acute toxicity tests in healthy mice, and 6.5-fold higher in tumor-bearing mice. The prodrug demonstrated rapid blood clearance and was mainly excreted in urine. Finally, compound proved effective *in vivo* in a mouse xenograft model of doxorubicin-resistant colorectal carcinoma LS 174T following i.v. administration.

SOURCE – Corixa.

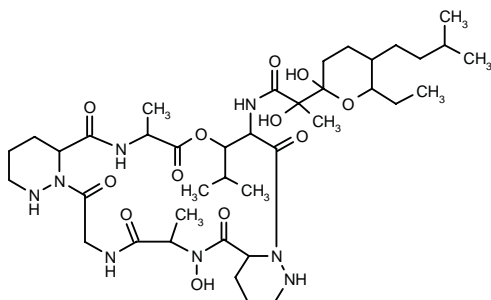
REFERENCES

1. Pickford, L.B. et al. (Corixa Corp.) *Prodrug cpds. with isoleucine*. WO 0195943.

PIPALAMYCIN

315327

2-[2-[*N*-[2-[6-Ethyl-2-hydroxy-5-(3-methylbutyl)-2*H*-pyran-2-yl]-2-hydroxy-2-methylacetyl]-3-hydroxy-leucyl]hexahydropyridazin-3-ylcarbonyl-*N*-hydroxy-alanyl-glycyl]-hexahydropyridazin-3-ylcarbonyl-alanine (7→2)-lactone



C39 H66 N8 O12; Mol wt: 838.9944

ACTION – Apoptosis inducer, a cyclic hexadepsipeptide isolated from the culture broth of *Streptomyces* sp. ML297-90F8. In apoptosis-resistant human pancreatic adenocarcinoma AsPC-1 cells, compound (3 µg/ml) produced apoptosis within 24-48 h and inhibited the growth of these cells with an IC₅₀ of 0.03 µg/ml after 3-day exposure. Its apoptosis-inducing activity appeared to involve activation of caspases. Compound also exhibited antibacterial activity against Gram-positive bacteria including *Staphylococcus aureus* and *Micrococcus luteus*.

SOURCES – Keio University, Yokohama (JP); Microbial Chemistry Research Foundation, Tokyo (JP).

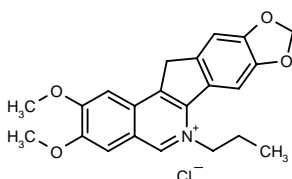
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DNA-INTERCALATING DRUGS

313256

2,3-Dimethoxy-6-propyl-12*H*-[1,3]dioxolo[5,6]indeno-[1,2-*c*]isoquinolin-6-ium chloride



C22 H22 Cl N O4; Mol wt: 399.8718

ACTION – Topoisomerase I inhibitor with cytotoxic activity against a panel of human cancer cell lines in the NCI screen. Compound exhibited *in vivo* anticancer activity in the hollow fiber assay against a panel of 12 tumor cell lines; it was particularly active against lung cancer NCI-H522 and ovarian cancer OVCAR-3 cells.

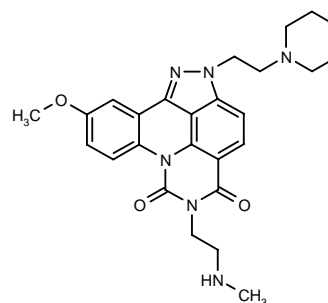
SOURCES – National Cancer Institute, Bethesda, MD (US); Purdue University, West Lafayette, IN (US).

REFERENCES

1. Cushman, M.S. et al. (Purdue Research Foundation; US Department of Health & Human Services) *Novel indenoisoquinolines as antineoplastic agents*. EP 1123099, WO 0021537.
2. Jayaraman, M. et al. *Synthesis of new dihydroindeno[1,2-*c*]isoquinoline and indenoisoquinolinium chloride topoisomerase I inhibitor having high in vivo anticancer activity in the hollow fiber animal model*. *J Med Chem* 2002, 45(1): 242.

314646

11-Methoxy-6-[2-(methylamino)ethyl]-2-[2-(1-piperidinyl)-ethyl]pyrazolo[3,4,5-*mn*]pyrimido[5,6,1-*de*]acridine-5,7(2*H*,6*H*)-dione



C26 H30 N6 O3; Mol wt: 474.5620

ACTION – Acridine derivative, an antineoplastic agent with broad-spectrum DNA-binding cytotoxic activity against a panel of NCI human cancer cells including human colon adenocarcinoma HT-29 cells (IC₅₀ = 0.04 nM). Compound did not show crossresistance with doxorubicin.

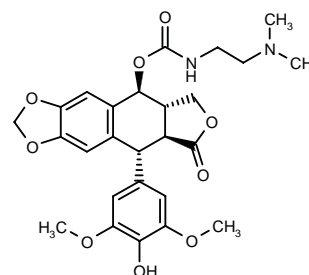
SOURCE – Novuspharma.

REFERENCES

1. Antonini, I. et al. 2,6-Di(*ω*-aminoalkyl)-2,5,6,7-tetrahydropyrazolo[3,4,5-*mn*]pyrimido[5,6,1-*de*]acridine-5,7-diones: Novel, potent, cytotoxic, and DNA-binding agents. *J Med Chem* 2002, 45(3): 696.

314697

N-[2-(Dimethylamino)ethyl]carbamic acid (5*S*,5*aS*,8*aS*,9*R*)-9-(4-hydroxy-3,5-dimethoxyphenyl)-8-oxo-5,5*a*,6,8,8*a*,9-hexahydrofuro[3',4':6,7]naphtho[2,3-*d*][1,3]dioxol-5-ylester



C26 H30 N2 O9; Mol wt: 514.5280

ACTION – Podophyllotoxin derivative with antiproliferative activity against murine leukemia L1210, human epidermoid carcinoma A-431, human lung carcinoma A549 and H69, human colon adenocarcinoma HT-29 and human oral epidermoid carcinoma KB-3-1 cells, giving respective IC₅₀ values of 0.038, 0.071, 0.046, 0.096, 0.121 and 0.085 µM. When given i.v. to mice bearing P388 tumors (6.25 mg/kg) and Lewis lung tumors (3.12 mg/kg), compound gave T/C values of 203 and 168%, respectively.

SOURCE – Servier.

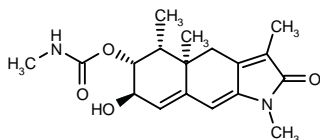
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HORMONAL AGENTS

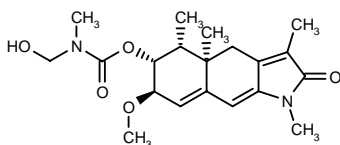
313662

N-Methylcarbamic acid 7(*R*)-hydroxy-1,3,4a(*R*),5(*R*)-tetramethyl-2-oxo-2,4,4a,5,6,7-hexahydro-1*H*-benzo[*f*]indol-6(*R*)-yl ester



C18 H24 N2 O4; Mol wt: 332.3976

ACTION – A metabolically stable progesterone receptor antagonist, expected to be useful for the treatment of hormone-dependent cancer, endometriosis, meningioma, osteoporosis and climacteric disturbances, and also as an abortifacient and oral contraceptive. Another exemplified benzo[*f*]indole-2-one is:



313663: C20 H28 N2 O5

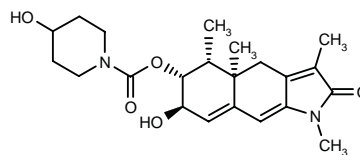
SOURCE – Meiji Seika.

REFERENCES

1. Kurihara, K. et al. (Meiji Seika Kaisha, Ltd.) *Novel tetrahydrobenzindolone derivs. and their preparation method*. JP 2001316364.

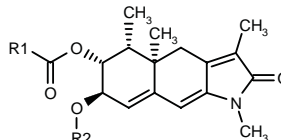
313664

4-Hydroxypiperidine-1-carboxylic acid 7(*R*)-hydroxy-1,3,4a(*R*),5(*R*)-tetramethyl-2-oxo-2,4,4a,5,6,7-hexahydro-1*H*-benzo[*f*]indol-6(*R*)-yl ester



C22 H30 N2 O5; Mol wt: 402.4880

ACTION – A metabolically stable progesterone receptor antagonist, expected to be useful for the treatment of hormone-dependent cancer, endometriosis, meningioma, osteoporosis and climacteric disturbances, and also as an abortifacient and oral contraceptive. Other exemplified benzo[*f*]indole-2-ones are:



Compound	R1	R2	Formula
313665	3-OH-1-pyrrolidinyl	Me	C ₂₂ H ₃₀ N ₂ O ₅
313666	4-OH-1-Pip	Me	C ₂₃ H ₃₂ N ₂ O ₅
313667	4-F-1-Pip	Me	C ₂₃ H ₃₁ FN ₂ O ₄
313668	4-F-Ph	H	C ₂₃ H ₂₄ FN ₂ O ₄
313669	3-OH-1-pyrrolidinyl	H	C ₂₁ H ₂₈ N ₂ O ₅
313670	3-F-1-pyrrolidinyl	H	C ₂₁ H ₂₇ FN ₂ O ₄
313671	4-F-1-Pip	H	C ₂₂ H ₂₉ FN ₂ O ₄

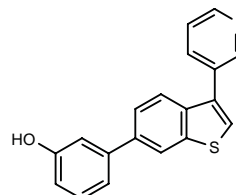
SOURCE – Meiji Seika.

REFERENCES

1. Kurihara, K. et al. (Meiji Seika Kaisha, Ltd.) *Stable novel tetrahydrobenzindolone derivs. and their preparation method*. JP 2001316363.

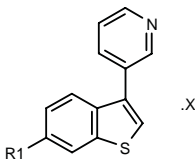
313936

3-[3-(3-Pyridyl)-1-benzothien-6-yl]phenol



C19 H13 N O S; Mol wt: 303.3837

ACTION – Agent with the ability to inhibit the enzyme 17α-hydroxylase/C₁₇₋₂₀ lyase (steroid 17-α-monooxygenase; 100% inhibition *in vitro*), potentially useful for the treatment of hormone-dependent disorders such as prostate cancer, prostatic hypertrophy, premature alopecia, endometriosis and breast, ovarian or uterine cancer. Other exemplified benzothiophene derivatives are:



Compound	R1	X	Formula
313938	3-Pyr		C ₁₈ H ₁₂ N ₂ S
313939	3-NH2-Ph		C ₁₉ H ₁₄ N ₂ S
313940	cyclobutyl-O	HCl	C ₁₇ H ₁₅ NOS.HCl
313942	3-thienyl	HCl	C ₁₇ H ₁₁ NS ₂ .HCl
313943	3-furyl	HCl	C ₁₇ H ₁₁ NOS.HCl
313944	2-thienyl	HCl	C ₁₇ H ₁₁ NS ₂ .HCl
313947	2-furyl	HCl	C ₁₇ H ₁₁ NOS.HCl
313948	i-Bu	HCl	C ₁₇ H ₁₇ NS.HCl

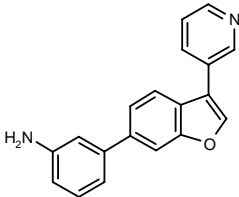
SOURCE – Snow Brand.

REFERENCES

1. Shimada, S. et al. (Snow Brand Milk Products Co., Ltd.) *Novel benzothiophene derivs.* WO 0187878.

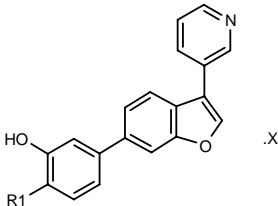
313949

3-[3-(3-Pyridyl)-1-benzofuran-6-yl]phenylamine



C19 H14 N2 O; Mol wt: 286.3326

ACTION – Agent with the ability to inhibit the enzyme 17α-hydroxylase/C₁₇₋₂₀ lyase (17-α-monooxygenase; 90% inhibition *in vitro*), potentially useful for the treatment of hormone-dependent disorders such as prostate cancer, prostatic hypertrophy, premature alopecia, endometriosis and breast, ovarian or uterine cancer. Other exemplified benzofuran derivatives are:



Compound	R1	X	Formula
313950	H		C ₁₉ H ₁₃ NO ₂
313951	OH	HBr	C ₁₉ H ₁₃ NO ₃ .HBr

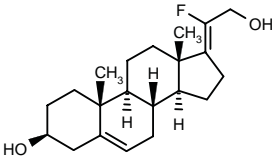
SOURCE – Snow Brand.

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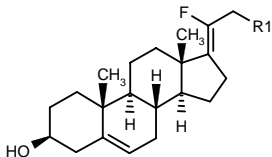
314863

(3β,17Z)-20-Fluoropregna-5,17-diene-3,21-diol



C21 H31 F O2; Mol wt: 334.4719

ACTION – An inhibitor of steroid 17α-hydroxylase/C_{17,20} lyase (steroid 17-α-monooxygenase) and/or 5α-reductase, potentially useful for the treatment of androgen- and estrogen-mediated diseases including breast cancer, polycystic ovary syndrome, prostatic hyperplasia, prostatic cancer, virilism, hirsutism, Cushing's syndrome and acne. Compound was shown to inhibit C_{17,20} lyase in monkey testicle preparations by 94% at 1 mM. Other exemplified 20-fluoro-substituted steroids are:



Compound	R1	Isomer	Formula
314864	OH	17E	C ₂₁ H ₃₁ FO ₂
314865	H	17Z	C ₂₁ H ₃₁ FO
314866	H	17E	C ₂₁ H ₃₁ FO

SOURCE – Aventis Pharma.

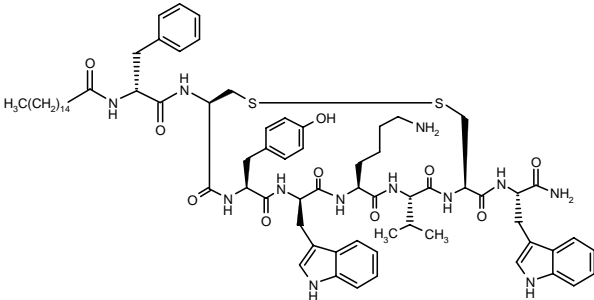
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PALMITOYL-RC-160

314602

N-Hexadecanoyl-D-phenylalanyl-L-cysteinyl-L-tyrosyl-D-tryptophyl-L-lysyl-L-valyl-L-cysteinyl-L-tryptophanamide cyclic (2-7)-disulfide



C73 H100 N12 O10 S2; Mol wt: 1369.7990

ACTION – Somatostatin analogue, a long-chain lipopeptide derivative of RC-160 with slightly higher affinity for somatostatin receptors (IC_{50} = 0.42 and 0.52 μ g/ml, respectively, in human breast adenocarcinoma MCF-7 cells), as well as improved antiproliferative activity in MCF-7 cells and protein tyrosine kinase-inhibitory activity. Compound also showed improved stability and increased resistance toward proteolytic degradation in serum. Potentially useful for the treatment of breast cancer.

SOURCES – Dabur Research Foundation, Uttar Pradesh (IN); National Institute of Immunology, New Delhi (IN).

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CANCER IMMUNOTHERAPY

ANTI-G17 IMMUNOGEN

220675

Antigastrin immunogen composed of a synthetic nonapeptide derived from the amino terminal of human gastrin-17 conjugated by a peptide spacer to diphtheria toxoid and formulated as a water-in-oil emulsion

Antigastrin therapeutic vaccine
G17DT
G17(9)-DT
Gastrimmune™

ACTION – Antigastrin vaccine for the treatment of cancer that neutralizes (blocks) both gastrin 17 and gly-gastrin and removes them from the circulation. The vaccine showed a strong therapeutic effect on established colon tumors in rats bearing syngeneic colon tumors, where it strongly reduced tumor area and final tumor size. Passive immunization of nude mice bearing human colorectal cancer metastases produced 30% inhibition of primary tumors and inhibited secondary spread by 70%. Results of a phase I/II clinical trial in patients with advanced colorectal cancer showed that the vaccine was well tolerated and induced measurable antibody titers in over 95% of patients; tumor burden did not regress significantly but treatment significantly increased median survival time from 184 to 338 days. It is currently in phase III evaluation for pancreatic cancer and phase II trials for gastric, esophageal and colorectal cancer.

SOURCES – Aphton; Aventis Pasteur.

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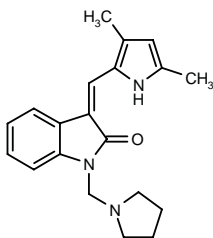
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INHIBITORS OF SIGNAL TRANSDUCTION PATHWAYS

313574

(Z)-3-(3,5-Dimethyl-1*H*-pyrrol-2-ylmethylene)-1-(pyrrolidin-1-ylmethyl)-2,3-dihydro-1*H*-indol-2-one



C20 H23 N3 O; Mol wt: 321.4217

ACTION – A representative compound from a series of indolinone derivatives that inhibit protein kinases, particularly receptor and nonreceptor tyrosine kinases and serine/threonine kinases. Potentially useful for the treatment of cancer (in particular colorectal and lung cancer and Kaposi's sarcoma), arthritis, restenosis, hepatic cirrhosis, atherosclerosis, glomerulonephritis, diabetic nephropathy, malignant nephrosclerosis, thrombotic microangiopathy syndromes, transplant rejection, glomerulopathies, psoriasis, diabetes, wound healing, inflammation, neurodegenerative diseases and infectious diseases.

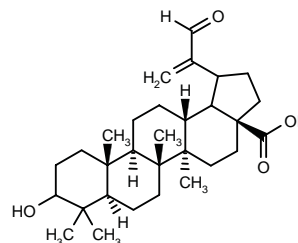
SOURCE – Pharmacia.

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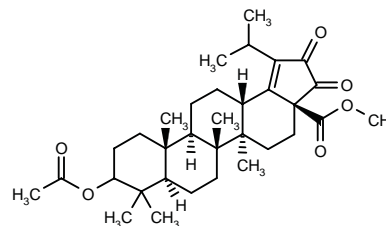
313725

3-Hydroxy-29-oxolup-20(30)-en-28-oic acid



C30 H46 O4; Mol wt: 470.6894

ACTION – Inhibitor of cyclin-dependent kinases (CDKs), able to interfere with the phosphorylation of the RB protein and therefore expected to be useful for the treatment of proliferative disorders, particularly cancer and leukemia. Compound demonstrated *in vitro* activity against a panel of cancer cell lines. Another exemplified triterpenoid compound is:



313726: C33 H48 O6

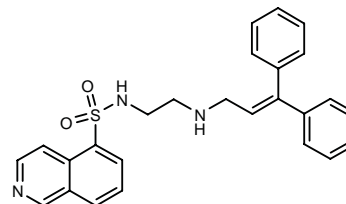
SOURCES – Cyclacel; Univerzita Karlova, Praha (CZ); Univerzita Palackeho, Olomouc (CZ).

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313999

N-[2-(3,3-Diphenyl-2-propenylamino)ethyl]isoquinoline-5-sulfonamide



C26 H25 N3 O2 S; Mol wt: 443.5685

ACTION – A selective inhibitor of protein kinase B (PKB), potentially useful for the treatment of cancer, diabetes, cardiovascular diseases, hemorrhagic shock, obesity, inflammatory diseases, CNS disorders and autoimmune diseases. This compound was also demonstrated to induce apoptosis *in vitro* and inhibited OVCAR-3 and U-87 MG cell growth.

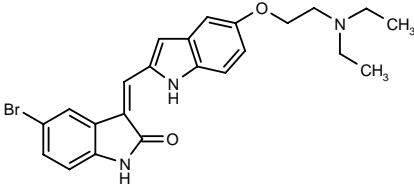
SOURCES – Peptor; Yissum.

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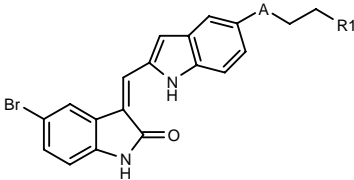
314251

(Z)-5-Bromo-3-[5-[2-(diethylamino)ethoxy]-1*H*-indol-2-ylmethylene]-2,3-dihydro-1*H*-indol-2-one



C23 H24 Br N3 O2; Mol wt: 454.3656

ACTION – Agent with the ability to modulate protein kinases and phosphatases, particularly tyrosine kinases. Potentially useful for the treatment of disorders related to abnormal tyrosine kinase signal transduction, particularly cancer. Other exemplified 2-indolinone compounds include the following:



Compound	R1	A	Formula
314252	N(Et)2	CH2	C ₂₄ H ₂₆ BrN ₃ O
314253	N(Me)2	O	C ₂₁ H ₂₀ BrN ₃ O ₂
314254	1-pyrrolidinyl	O	C ₂₃ H ₂₂ BrN ₃ O ₂

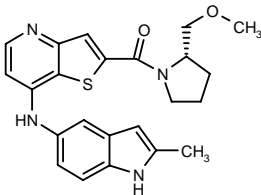
SOURCE – Sugen (Pharmacia).

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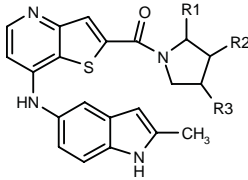
314354

1-[2(S)-(Methoxymethyl)pyrrolidin-1-yl]-1-[7-(2-methyl-1*H*-indol-5-ylamino)thieno[3,2-*b*]pyridin-2-yl]methanone



C23 H24 N4 O2 S; Mol wt: 420.5346

ACTION – Agent with the ability to modulate KDR/Fik-1 (vascular endothelial growth factor [VEGF]) receptor kinase and to inhibit the proliferation of endothelial cells. Potentially useful for the treatment of hyperproliferative disorders such as cancer and benign prostatic hyperplasia. Other specifically claimed thiophene derivatives are:



Compound	R1	R2	R3	Isomer	Formula
314355	H	N(Et)Ac	H	racemic	C ₂₅ H ₂₇ N ₅ O ₂ S
314356	H	N(Me)2	H	S	C ₂₃ H ₂₅ N ₅ OS
314357	H	N(Me)Ac	H	racemic	C ₂₄ H ₂₅ N ₅ O ₂ S
314358	CH2OMe	H	H	R	C ₂₃ H ₂₄ N ₄ O ₂ S
314359	H	OH	H	S	C ₂₁ H ₂₀ N ₄ O ₂ S
314360	H	OH	H	R	C ₂₁ H ₂₀ N ₄ O ₂ S
314361	H	cyclobutyl-CONH	H	racemic	C ₂₆ H ₂₇ N ₅ O ₂ S
314362	H	-CH(NH2)-			C ₂₂ H ₂₁ N ₅ OS
314363	H	OMe	H	S	C ₂₂ H ₂₂ N ₄ O ₂ S

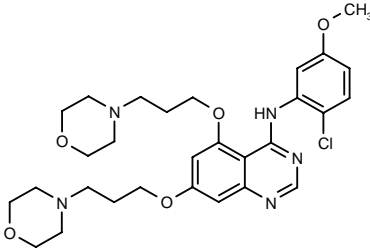
SOURCE – Pfizer.

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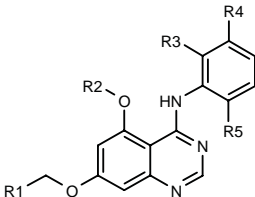
314379

N-(2-Chloro-5-methoxyphenyl)-5,7-bis[3-(4-morpholinyl)propoxy]quinazolin-4-amine



C29 H38 Cl N5 O5; Mol wt: 572.1022

ACTION – Antineoplastic agent that acts as a selective inhibitor of nonreceptor tyrosine kinases of the Src family including c-Src and c-Yes. Potentially useful for the treatment of solid tumors. Other specifically claimed 4-aminoquinazoline derivatives include the following:



Compound	R1	R2	R3	R4	R5	Formula
314380	4-Me-1-Piz-CH2CH2	4-THP	H	OMe	Cl	C ₂₈ H ₃₆ ClN ₅ O ₄
314382	4-morpholinyl-CH2CH2	4-THP	H	OMe	Cl	C ₂₇ H ₃₃ ClN ₄ O ₅
314384	4-morpholinyl-CH2CH2	3-THF	H	OMe	Cl	C ₂₆ H ₃₁ ClN ₄ O ₅
314385	H	4-Pip-CH2	H	OMe	Br	C ₂₂ H ₂₅ BrN ₄ O ₃
314386	1-pyrrolidinyl-CH2	4-THP	H	OMe	Br	C ₂₆ H ₃₁ BrN ₄ O ₄
314387	1-pyrrolidinyl-CH2	cyclopentyl	H	OMe	Br	C ₂₆ H ₃₁ BrN ₄ O ₃
314388	1-pyrrolidinyl-CH2	4-THP	-OCH2O-	Cl		C ₂₆ H ₂₉ ClN ₄ O ₅
314389	4-Pyr-OCH2	4-THP	-OCH2O-	Cl		C ₂₇ H ₂₅ ClN ₄ O ₆
314390	1-Me-4-Pip	4-THP	-OCH2O-	Cl		C ₂₇ H ₃₁ ClN ₄ O ₅

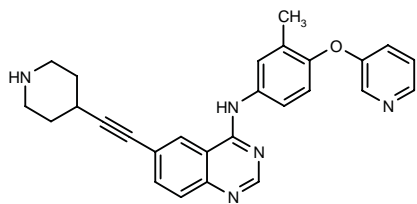
SOURCE – AstraZeneca.

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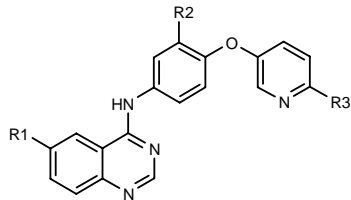
314758

N-[3-Methyl-4-(pyridin-3-yloxy)phenyl]-6-[2-(4-piperidinyl)-ethynyl]quinazolin-4-amine



C27 H25 N5 O; Mol wt: 435.5285

ACTION – Antitumor agent with the ability to inhibit receptor tyrosine kinases, as well as nonreceptor tyrosine kinases and serine threonine kinases. Other exemplified 4-phenylaminoquinazolines are:



Compound	R1	R2	R3	Formula
314759	ethynyl-CH2NHCOCH2Cl	Me	H	C ₂₅ H ₂₀ ClN ₅ O ₂
314760	ethynyl-CH2NHCOCH2N(Me)2	Me	H	C ₂₇ H ₂₆ N ₆ O ₂
314761	ethynyl-CH2NHCONHMe	Cl	Me	C ₂₅ H ₂₁ ClN ₅ O ₂
314762	ethynylene-CH2OH	Me	H	C ₂₃ H ₁₈ N ₄ O ₂
314763	4-morpholinyl-CH2CH=CH	Me	H	C ₂₇ H ₂₇ N ₅ O ₂
314765	(E)-CH=CHCH2NHAc	Cl	Me	C ₂₅ H ₂₂ ClN ₅ O ₂
314766	(E)-2(S)-(MeOCH2)-1-pyrrolidinyl-CONHCH2CH=CH	Me	Me	C ₃₁ H ₃₄ N ₆ O ₃
314768	(E)-CH=CHCH2NHCOC(Me)2OH	Me	Me	C ₂₈ H ₂₉ N ₅ O ₃

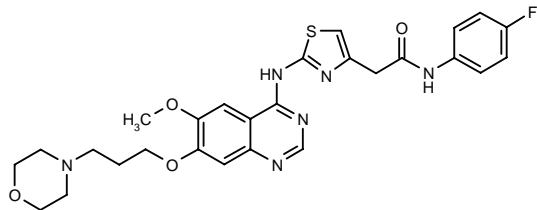
SOURCE – Pfizer.

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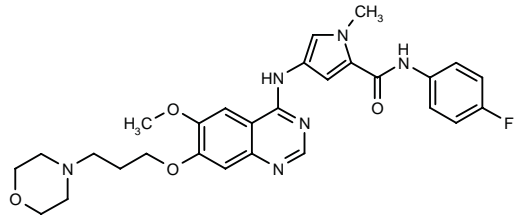
315063

N-(4-Fluorophenyl)-2-[2-[6-methoxy-7-[3-(4-morpholinyl)-propoxy]quinazolin-4-ylamino]thiazol-4-yl]acetamide



C27 H29 F N6 O4 S; Mol wt: 552.6281

ACTION – Agent with the ability to inhibit aurora2 kinase (50% inhibition at 0.167 μM), proven to prevent the growth of human breast cancer MCF-7 cells at 0.616 μM. In addition, it was shown to arrest cell cycle in the G2 phase following treatment of MCF-7 cells (> 50% of cells in G2/M phase vs. 9.27% in controls). Potentially useful for the treatment of proliferative diseases, particularly colorectal and breast cancer. Another exemplified substituted quinazoline derivative is:



315064: C28 H31 F N6 O4

SOURCE – AstraZeneca.

REFERENCES

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FALNIDAMOL

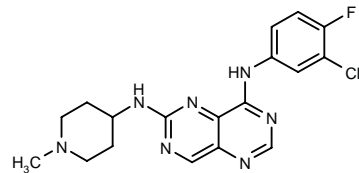
Prop INN

285679

8-(3-Chloro-4-fluorophenylamino)-2-(1-methyl-4-piperidinylamino)pyrimido[5,4-*d*]pyrimidine

*N*⁸-(3-Chloro-4-fluorophenyl)-*N*²-(1-methyl-4-piperidinyl)pyrimido[5,4-*d*]pyrimidine-2,8-diamine

BIBX-1382
BIBX-1382BS



C18 H19 Cl F N7; Mol wt: 387.8481

ACTION – Selective inhibitor of epidermal growth factor receptor (EGFR) tyrosine kinase (IC₅₀ = 3 nM) proven to efficiently penetrate the cell and inhibit EGF-induced EGFR autophosphorylation in a variety of human cancer cells including head and neck cancer HN5 and epidermoid carcinoma A-431 cells (IC₅₀ = 139 and 372 nM, respectively). Compound also inhibited TGF-α-stimulated mitogenesis in human epidermoid carcinoma KB cells with an IC₅₀ of 150 nM. Anticancer activity was seen against various human solid tumors implanted in nude mice at doses of 10-70 mg/kg/day, and long-term treatment with compound at a dose of 50 mg/kg/day p.o. produced marked tumor regression in the A-431 and HN5 xenograft models.

SOURCE – Boehringer Ingelheim.

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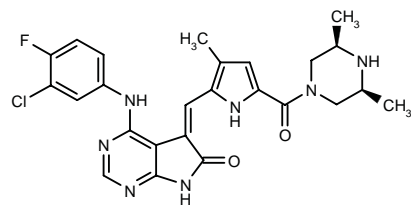
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SU-11925

316717

4-(3-Chloro-4-fluorophenylamino)-5(Z)-[5-[3(R),5(S)-dimethylpiperazin-1-ylcarbonyl]-3-methyl-1 H-pyrrol-2-ylmethylene]-6,7-dihydro-5H-pyrrolo[2,3-*d*]pyrimidin-6-one



C25 H25 Cl F N7 O2; Mol wt: 509.9705

ACTION – Dual inhibitor of epidermal growth factor receptor (EGFR) and HER-2 tyrosine kinase (IC₅₀ = 30 and 38 nM, respectively), proven to inhibit EGF-stimulated EFGR phosphorylation and tumor growth in mice bearing human epidermoid carcinoma A-431 at a dose of 100 mg/kg p.o. Approximately 10-fold higher plasma concentrations of compound were required to inhibit HER-2-phosphorylation in HER-2-dependent xenografts compared with EGFR phosphorylation in EGFR-overexpressing tumors *in vivo*.

SOURCE – Sugen (Pharmacia).

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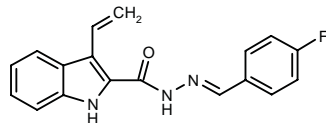
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ANGIOGENESIS INHIBITORS

313547

N'-(4-Fluorobenzylidene)-3-vinyl-1 H-indole-2-carbohydrazide



C18 H14 F N3 O; Mol wt: 307.3266

ACTION – Angiogenesis inhibitor, potentially useful for the treatment of primary and metastatic solid tumors, diabetic retinopathy, corneal graft rejection and psoriasis, among other disorders.

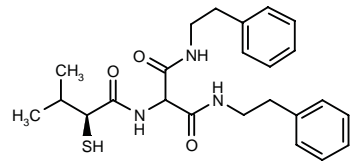
SOURCE – Abbott.

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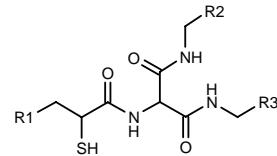
313680

2-[3-Methyl-2(S)-sulfanylbutyramido]-N,N'-bis(2-phenylethyl)malonamide



C24 H31 N3 O3 S; Mol wt: 441.5929

ACTION – Matrix metalloproteinase (MMP) inhibitor, considered to have potential in the treatment of cancer, arthritis, osteoporosis and chronic inflammatory disorders, particularly emphysema. Other specifically claimed amidomalonomides include the following:



Compound	R1	R2=R3	Isomer	Formula
313681	Ph	Ph	S	C ₂₆ H ₂₇ N ₃ O ₃ S
313682	Ph	4-MeO-PhCH ₂	S	C ₃₀ H ₃₅ N ₃ O ₅ S
313683	H	CH ₂ Ph	S	C ₂₂ H ₂₇ N ₃ O ₃ S
313684	Ph	4-Cl-PhCH ₂		C ₂₈ H ₂₉ Cl ₂ N ₃ O ₃ S
313685	Ph	4-Me-PhCH ₂	S	C ₃₀ H ₃₅ N ₃ O ₃ S
313686	Ph	3-MeO-PhCH ₂		C ₃₀ H ₃₅ N ₃ O ₅ S
313687	Ph	3-Cl-PhCH ₂		C ₂₈ H ₂₉ Cl ₂ N ₃ O ₃ S
313688	Ph	3,4-(Cl) ₂ -PhCH ₂		C ₂₈ H ₂₇ Cl ₄ N ₃ O ₃ S

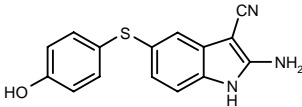
SOURCE – Aventis Pharma.

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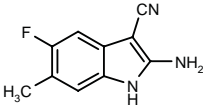
314054

2-Amino-5-(4-hydroxyphenylsulfanyl)-1*H*-indole-3-carbonitrile



C15 H11 N3 O S; Mol wt: 281.3379

ACTION – Tubulin-binding agent with antiangiogenic activity, found to inhibit colchicine binding to tubulin by 36% at 10 μ M; at 100 μ M, it inhibited by 55% the adhesion of human umbilical vein endothelial cells (HUVEC) to a solid support. Potentially useful for the treatment of conditions associated with angiogenesis including cancer, diabetes, psoriasis, rheumatoid arthritis, Kaposi's sarcoma, hemangioma, acute and chronic nephropathies, atheroma, arterial restenosis, autoimmune diseases, acute inflammation, endometriosis, dysfunctional uterine bleeding and ocular diseases with retinal vessel proliferation. Another exemplified 2-amino-3-cyanoindole derivative is:



314055: C10 H8 F N3

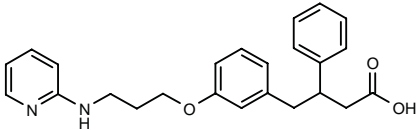
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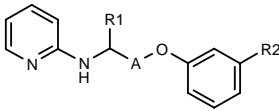
314620

3-Phenyl-4-[3-[3-(pyridin-2-ylamino)propoxy]phenyl]-butyric acid



C24 H26 N2 O3; Mol wt: 390.4804

ACTION – An $\alpha_v\beta_3$ (vitronectin) and/or $\alpha_v\beta_5$ integrin receptor antagonist, potentially useful for the treatment of cancer, angiogenesis, osteoporosis, humoral hypercalcemia, smooth muscle cell migration, restenosis, atherosclerosis, macular degeneration, retinopathy and arthritis. Other exemplified compounds are:



Compound	R1	R2	A	Formula
314621	H	SO2NHCH(Ph)CH2CO2H	-(CH2)3-	C ₂₄ H ₂₇ N ₃ O ₅ S
314622	Me	SO2CH2CH(Ph)CH2CO2H	-(CH2)2-	C ₂₅ H ₂₈ N ₂ O ₅ S
314623	Me	SO2CH2CH(4-F-Ph)CH2CO2H	-(CH2)2-	C ₂₅ H ₂₇ FN ₂ O ₅ S
314624	H	SO2NHCH2CH2CO2H	-(CH2)3-	C ₁₈ H ₂₃ N ₃ O ₅ S
314625	H	SO2NHCH(Me)CH2CO2H	-(CH2)3-	C ₁₉ H ₂₅ N ₃ O ₅ S
314626	H	SO2NHCH(Ph)CH2CO2H	-(CH2)4-	C ₂₅ H ₂₈ N ₃ O ₅ S
314628	H	(S)-2-(NH2SO2)-Ph-ethynylene-CH(CH2CO2H)NHSO2	-(CH2)3-	C ₂₆ H ₂₈ N ₄ O ₇ S ₂
314629	H	CH2CH(Ph)CH2CO2H	-(CH2)2-	C ₂₄ H ₂₆ N ₂ O ₃

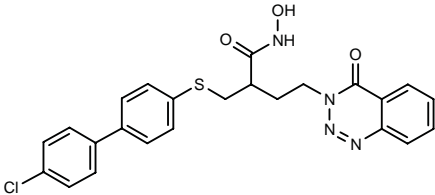
SOURCE – Pharmacia.

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315349

2-(4'-Chlorobiphenyl-4-ylsulfanylmethyl)-4-(4-oxo-3,4-dihydro-1,2,3-benzotriazin-3-yl)butyroxamic acid



C24 H21 Cl N4 O3 S; Mol wt: 480.9739

ACTION – Gelatinase A (MMP-2) inhibitor (IC_{50} = 0.06 nM) with less activity against gelatinase B (MMP-9; IC_{50} = 0.5 nM) and high selectivity over interstitial collagenase (MMP-1; IC_{50} > 100 μ M), stromelysin 1 (MMP-3; IC_{50} = 10 nM) and collagenase 3 (MMP-13; IC_{50} = 1.2 nM). In mice bearing melanoma B16F10, doses of 100 and 200 mg/kg i.p. produced a significant reduction in tumor burden (45 and 55%, respectively) and a marked reduction in size of metastases (50 and 100%, respectively). Compound exhibited modest stability in human hepatic microsomes and high permeability in Caco-2 cells.

SOURCE – Servier.

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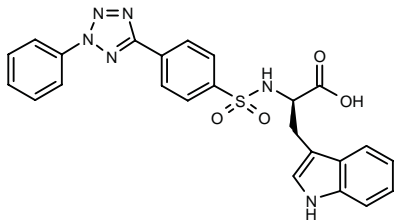
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MMI-166*

260690

N-[4-(2-Phenyl-2H-tetrazol-5-yl)phenylsulfonyl]-D-trypto-
phan



C24 H20 N6 O4 S; Mol wt: 488.5260

ACTION – Potent inhibitor of human matrix metalloproteinases (MMPs) with high selectivity for gelatinase A (MMP-2; IC₅₀ = 0.4 nM), gelatinase B (MMP-9; IC₅₀ = 90 nM) and MMP-15 (IC₅₀ = 100 nM) over other MMPs (IC₅₀ > 0.4 μM), proven to inhibit angiogenesis without showing cytotoxic activity in hamster pancreatic PGHAM-1 cells. In nude mice, compound strongly inhibited metastatic colonization of murine Lewis lung carcinoma or human colon carcinoma C-1H cells by 43 and 63%, respectively. Moreover, it inhibited the growth of human gastric TMK-1 and murine melanoma B16-BL6 xenografts, and it prolonged survival of mice bearing human lung carcinoma Ma44 cells. The antitumor efficacy of compound is accompanied by a significant reduction in angiogenesis and an increase in apoptosis.

SOURCE – Shionogi.

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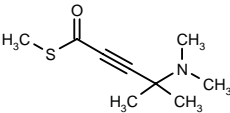
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*Identified compound **260690** Drug Data Rep 1998, 020(04): 0354.

OTHER ONCOLYTIC DRUGS

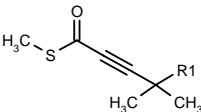
313992

4-(Dimethylamino)-4-methyl-2-pentynethioic acid *S*-meth-
yl ester



C9 H15 N O S; Mol wt: 185.2895

ACTION – Apoptosis inducer shown to inhibit the proliferation of a panel of cancer cell lines with IC₅₀ values in the low micromolar range. Potentially useful for the treatment of cancer, as well as dermatological conditions including acne, psoriasis, eczema, lupus erythematosus, etc. Its use in the treatment of arthritis and corneopathies is also described. Other exemplified aminothiolesters are:



Compound	R1	Formula
313993	N(Me)3 ⁺ T ⁻	C ₁₀ H ₁₈ INOS
313997	N(Pr)2	C ₁₃ H ₂₃ NOS
313998	1-pyrrolidinyl	C ₁₁ H ₁₇ NOS

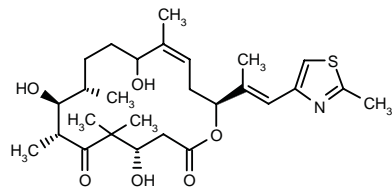
SOURCE – Galderma.

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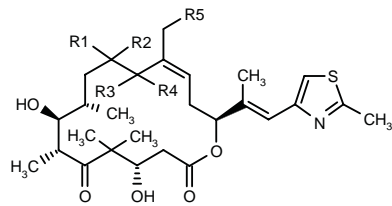
314000

(4*S*,7*R*,8*S*,9*S*,16*S*)-4,8,12-Trihydroxy-5,5,7,9,13-pentamethyl-16-[1-methyl-2-(2-methylthiazol-4-yl)vinyl]-oxacyclohexadec-13-ene-2,6-dione



C27 H41 N O6 S; Mol wt: 507.6879

ACTION – An epothilone derivative with antitumor activity. Potentially useful for the treatment of cancer and other hyperproliferative disorders. Other specifically claimed compounds are:



Compound	R1	R2	R3	R4	R5	Formula
314001	H	H	F	H	H	C ₂₇ H ₄₀ FN ₁ O ₆ S
314002	H	H	-O-		H	C ₂₇ H ₃₈ NO ₆ S
314003	H	H	H	-OCH2O-		C ₂₈ H ₄₁ NO ₇ S
314129		-O-	H	H	H	C ₂₇ H ₃₈ NO ₆ S

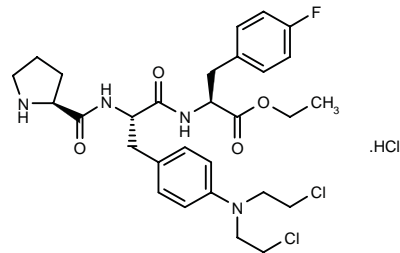
SOURCE – Kosan.

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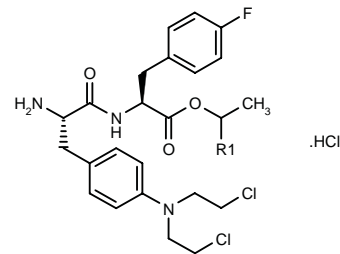
314586

L-Prolyl-4-[*N,N*-bis(2-chloroethyl)amino]-L-phenylalanyl-4-fluoro-L-phenylalanine ethyl ester hydrochloride



C29 H37 Cl2 F N4 O4 . HCl; Mol wt: 632.0002

ACTION – Antitumor agent, particularly useful for the treatment of breast, lung and ovarian cancer, leukemia, lymphoma and multiple myeloma. It demonstrated *in vitro* activity against a panel of human tumor cell lines and was shown to circumvent melphalan resistance. Other exemplified melphalan-containing peptides are:



Compound	R1	Formula
314587	H	C ₂₄ H ₃₀ Cl ₂ FN ₃ O ₃ .HCl
314588	Me	C ₂₅ H ₃₂ Cl ₂ FN ₃ O ₃ .HCl

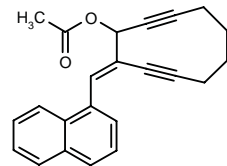
SOURCE – Oncopeptides.

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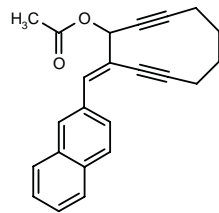
314977

Acetic acid 10-(naphthalen-1-ylmethylene)-2,8-cyclo-decadiyn-1-yl ester



C23 H20 O2; Mol wt: 328.4090

ACTION – Eenedyne prodrug with cytotoxic activity against murine lymphocytic leukemia P388 cells (IC₅₀ = 2.4 μM) and strong DNA-cleaving activity. Another related compound is:



314978: C23 H20 O2

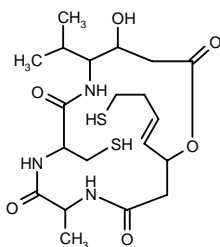
SOURCES – Hong Kong University of Science & Technology, Kowloon (HK); Kyoto University, Kyoto (JP).

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315142

13-Hydroxy-12-isopropyl-6-methyl-2-(4-sulfanyl-1-buten-yl)-9-(sulfanylmethyl)-1-oxa-5,8,11-triazacyclopentadecane-4,7,10,15-tetraone



C20 H33 N3 O6 S2; Mol wt: 475.6277

ACTION – Antitumor agent that inhibits histone deacetylase and was shown to inhibit the proliferation of a panel of human cancer cell lines.

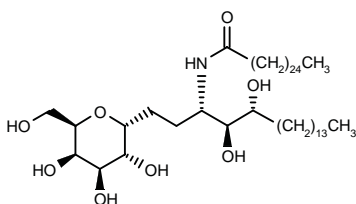
SOURCE – Yamanouchi.

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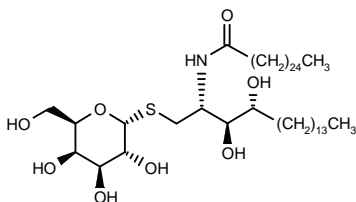
315143

N-[1(*S*)-[2-(α -D-Galactopyranosyl)ethyl]-2(*S*),3(*R*)-dihydroxyheptadecyl]hexacosanamide



C51 H101 N O8; Mol wt: 856.3579

ACTION – A glycolipid derivative for use as an antitumor agent and immunostimulant. It was able to increase DNA synthesis in mouse spleen cells by 54.6% at 1 ng/ml. *In vivo*, it inhibited the metastasis of B16 melanoma xenografts by 65.3% following administration to mice at 0.001 mg/kg p.o. Another exemplified compound is:



315144: C50 H99 N O8 S

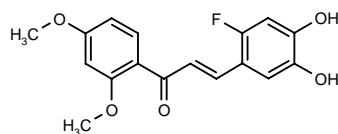
SOURCE – Kotobuki.

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315510

1-(2,4-Dimethoxyphenyl)-3-(2-fluoro-4,5-dihydroxyphenyl)-2-propen-1-one



C17 H15 F O5; Mol wt: 318.2985

ACTION – Antineoplastic agent, a 5-lipoxygenase inhibitor (IC_{50} = 87 nM in rat basophilic leukemia RBL-1 cells) able to inhibit Fe^{3+} ADP-induced lipid peroxidation in rat liver microsomes with an IC_{50} value of 3.5 μ M. Compound exhibited strong cytotoxic activity against a panel of human cancer cells including breast adenocarcinoma MCF-7 and ovarian carcinoma OVCAR-3 cells (IC_{50} = 0.55 and 0.53 μ M, respectively).

SOURCES – National Institutes of Health, Bethesda, MD (US); University of Tokushima, Tokushima (JP); Tokushima Bunri University, Tokushima (JP); Tokyo University of Pharmacy and Life Science, Tokyo (JP); Toyama Medical and Pharmaceutical University, Toyama (JP).

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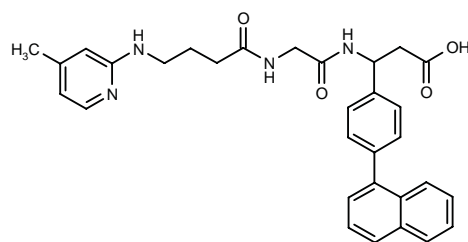
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315924

3-[*N*-[4-(4-Methylpyridin-2-ylamino)butyryl]glycylamino]-3-[4-(1-naphthyl)phenyl]propionic acid

N-[4-(4-Methylpyridin-2-ylamino)butyryl]glycyl-3-[4-(1-naphthyl)phenyl]- β -alanine



C31 H32 N4 O4; Mol wt: 524.6178

ACTION – Potent, specific, small-molecule inhibitor of $\alpha_v\beta_6$ integrin (IC_{50} = 0.04 nM) with high selectivity over $\alpha_v\beta_5$, $\alpha_v\beta_3$ and $\alpha_{IIb}\beta_3$ integrins (IC_{50} = 5170, 8 and 4230 nM, respectively); its selectivity for $\alpha_v\beta_6$ was also demonstrated in cell adhesion assays, where it gave respective IC_{50} values of 0.2, 20 and 3 μ M for $\alpha_v\beta_6$, $\alpha_v\beta_5$ and $\alpha_v\beta_3$. Potentially useful for the treatment of cancer.

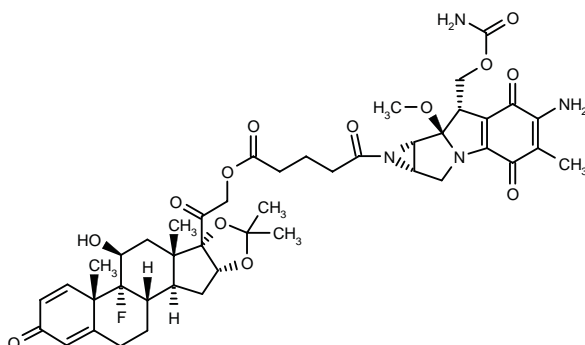
SOURCE – Merck KGaA.

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315962

5-[(1*a*S,8*S*,8*a*R,8*b*S)-6-Amino-8-(carbamoyloxymethyl)-8*a*-methoxy-5-methyl-4,7-dioxo-1,1*a*,2,4,7,8,8*a*,8*b*-octahydroazirino[2',3':3,4]pyrrolo[1,2-*a*]indol-1-yl]-5-oxopentanoic acid 9-fluoro-11β-hydroxy-16α,17-(isopropylidenedioxy)-3,20-dioxopregna-1,4-dien-21-yl ester



C44 H53 F N4 O13; Mol wt: 864.9157

ACTION – Mitomycin C and triamcinolone acetonide conjugate with antiproliferative activity in NIH/3T3 fibroblasts comparable to that of mitomycin ($IC_{50} = 2.4$ and $1.7 \mu M$, respectively). In aqueous solution, the conjugate was hydrolyzed and the single components were released slowly in equimolar concentrations, with a calculated half-life of 23.6 h. No toxicity was seen in rats after intravitreal administration of the conjugate. Potentially useful for the treatment of proliferative diseases affecting cavitory organs where the short half-life of the individual components limits their clinical use.

SOURCE – Medical University of South Carolina, Charleston, SC (US).

REFERENCES

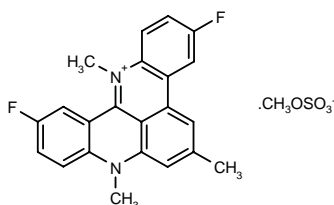
1. Macky, T.A. et al. *Synthesis, pharmacokinetics, efficacy, and rat retinal toxicity of a novel mitomycin C-triamcinolone acetonide conjugate.* J Med Chem 2002, 45(5): 1122.

RHPS4¹⁻⁵

301622

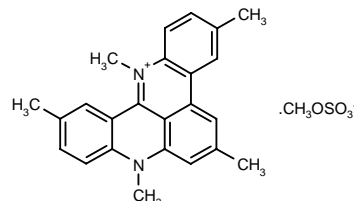
3,11-Difluoro-6,8,13-trimethyl-8*H*-quino[4,3,2-*k*]acridin-13-ium methylsulfate

NSC-714187



C22 H17 F2 N2 . C H3 O4 S; Mol wt: 458.4830

ACTION – Potent inhibitor of telomerase ($IC_{50} = 0.33 \mu M$) that acts by stabilizing 4-stranded G-quadruplex structures formed by single-stranded telomeric DNA. Compound exhibited low acute cytotoxicity against a panel of human cancer cells; the mean IC_{50} after 4-day exposure was $7.02 \mu M$, about 20 times higher than the concentration required for inhibition in the TRAP (telomeric repeat amplification protocol) assay. In contrast, long-term exposure of breast cancer 21NT cells and human vulvar epidermoid carcinoma A-431 cells to nonacute cytotoxic concentrations of compound produced a marked decrease in cell growth after 15 days, concomitant with a reduction in telomerase activity. Another related compound is:



RHPS3 [302378]^{4,5}: C24 H23 N2 . C H3 O4 S
NSC-714186

SOURCES – Institute of Cancer Research, London (GB); University of Nottingham, Nottingham (GB).

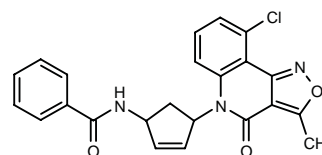
REFERENCES

1. Gavathiotis, E. et al. *Recognition and stabilization of quadruplex DNA by a potent new telomerase inhibitor: NMR studies of the 2:1 complex of a pentacyclic methylacridinium cation with d(TTAGGGT)4.* Angew Chem Int Ed 2001, 40(24): 4749.
2. Gowan, S.M. et al. *Potent inhibition of telomerase by small-molecule pentacyclic acridines capable of interacting with G-quadruplexes.* Mol Pharmacol 2001, 60(5): 981.
3. Gowan, S.M. et al. *Preclinical antitumor properties of G-quadruplex interactive small molecule inhibitors of telomerase.* Proc Amer Assoc Cancer Res 2001, 42: Abst 466.
4. Heald, R.A. et al. *Antitumor polycyclic acridines. 8. Synthesis and telomerase-inhibitory activity of methylated pentacyclic acridinium salts.* J Med Chem 2002, 45(3): 590.
5. Stevens, M.F.G. et al. *Synthesis of novel pentacyclic methylacridinium salts as potential telomerase inhibitors and their interactions with duplex, triplex and quadruplex DNA.* Proc Amer Assoc Cancer Res 2001, 42: Abst 4465.

MODULATORS OF THE THERAPEUTIC ACTIVITY OF ANTINEOPLASTIC AGENTS

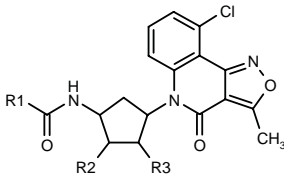
314415

N-[4-(9-Chloro-3-methyl-4-oxo-4,5-dihydroisoxazolo-[4,3-*c*]quinolin-5-yl)-2-cyclopenten-1-yl]benzamide

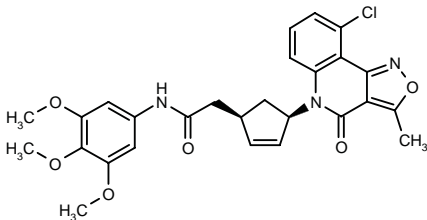


C23 H18 Cl N3 O3; Mol wt: 419.8662

ACTION – A multidrug resistance protein MRP-1 inhibitor, potentially useful as an oncolytic, particularly for the therapy of neoplasms with intrinsic or acquired resistance. Other exemplified tricyclic compounds are:



Compound	R1	R2	R3	Formula
314416	NHPh	bond		C ₂₃ H ₁₉ ClN ₄ O ₃
314418	3,4,5-(MeO)3-PhCO	bond		C ₂₇ H ₂₄ ClN ₃ O ₇
314420	3,4,5-(MeO)3-PhNH	bond		C ₂₆ H ₂₅ ClN ₄ O ₆
314421	CH2Ph	bond		C ₂₄ H ₂₀ ClN ₃ O ₃
314423	2-MeO-PhCH2	bond		C ₂₆ H ₂₂ ClN ₃ O ₄
314426	3,4,5-(MeO)3-PhCH2	bond		C ₂₇ H ₂₆ ClN ₃ O ₆
314427	3-F-PhCH2	bond		C ₂₄ H ₁₉ ClFN ₃ O ₃
314431	(R)-t-BuOCONHCH(Ph)	bond		C ₂₉ H ₂₉ ClN ₄ O ₅
314435	3,4,5-(MeO)3-PhCH2	OH	OH	C ₂₇ H ₂₆ ClN ₃ O ₈
314440	3,4,5-(MeO)3-PhCH2	-OC(Me)2O-		C ₃₀ H ₃₂ ClN ₃ O ₈
314441	3-F-PhCH2	OH	OH	C ₂₄ H ₂₁ ClFN ₃ O ₅
314446	3-F-PhCH2	-OC(Me)2O-		C ₂₇ H ₂₆ ClFN ₃ O ₅
314567	(S)-t-BuOCONHCH(Ph)	bond		C ₂₉ H ₂₉ ClN ₄ O ₅



314451: C27 H26 Cl N3 O6

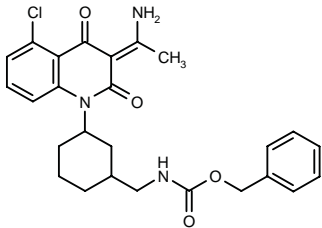
SOURCE – Lilly.

REFERENCES

1. Lander, P.A. et al. (Eli Lilly and Company) *Tricyclic cpds. as MRP1-inhibitors*. WO 0196346.

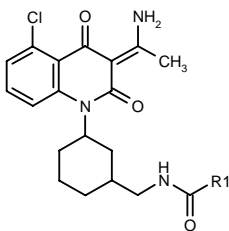
314867

N-[3-[3-(1-Aminoethylidene)-5-chloro-2,4-dioxo-1,2,3,4-tetrahydroquinolin-1-yl]cyclohexylmethyl]carbamic acid benzyl ester



C26 H28 Cl N3 O4; Mol wt: 481.9772

ACTION – Multidrug resistance protein (MRP-1) inhibitor, potentially useful for overcoming multidrug resistance in neoplasms. Other exemplified 5-chloro-1-cyclohexyl-1,2,3,4-quinolin-2,4-diones are:



Compound	R1	Formula
314868	3-Pyr	C ₂₄ H ₂₅ ClN ₄ O ₃
314869	6-F-3-Pyr	C ₂₄ H ₂₄ ClFN ₄ O ₃
314870	Ph	C ₂₅ H ₂₆ ClN ₃ O ₃

SOURCE – Lilly.

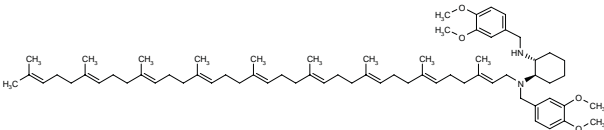
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1. Bonjouklian, R. and York, J.S. (Eli Lilly and Company) *Methods and cpds. for inhibiting MRP1*. WO 0200624.

N-5228*

257479

trans-(all E)-N,N'-Bis(3,4-dimethoxybenzyl)-N-(3,7,11,15,19,23,27,31,35-nonamethyl-2,6,10,14,18,22,26,30,34-hexatriacontanonaenyl)cyclohexane-1,2-diamine



C69 H106 N2 O4; Mol wt: 1027.6060

ACTION – Multidrug resistance modulator proven to reverse paclitaxel resistance in human bladder cancer cells.

SOURCE – Nisshin Seifun.

REFERENCES

1. Inomata, K. et al. (Nisshin Seifun Group Inc.) *Isoprene derivs*. EP 0787716, JP 1997268162.

2. Enokida, H. et al. *Reversal of Taxol resistance by a synthetic isoprenoid in human bladder cancer cell line*. Jpn J Cancer Res 2001, 92(Suppl.): Abst 1999.

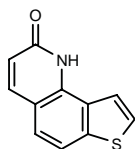
3. Nakagawa, M. et al. *Reversal of Taxol resistance by synthetic isoprenoids in human bladder cancer cell line*. Proc Amer Assoc Cancer Res 2001, 42: Abst 5129.

*Identified compound **257479** Drug Data Rep 1998, 020(06): 0547.

RADIATION THERAPY

315524

Thieno[2,3-*h*]quinolin-2(1*H*)-one



C₁₁ H₇ N O S; Mol wt: 201.2483

ACTION – Photochemotherapeutic agent proven to reduce DNA synthesis in murine Ehrlich ascites cells (after sensitization with 20 μ M), clonal growth of human cervical adenocarcinoma HeLa cells (after sensitization with 5 μ M) and to reduce the surviving fraction of the T2 bacteriophage (after sensitization with 2 μ M) in conjunction with UVA. No phototoxicity was seen in guinea pig skin.

SOURCES – Università degli Studi di Genova, Genova (IT); Università degli Studi di Padova, Padova (IT).

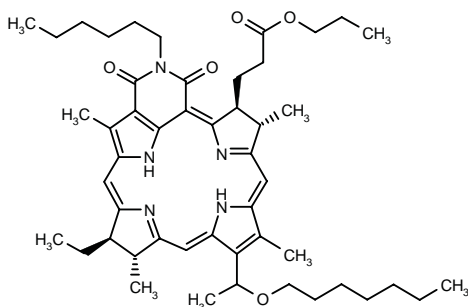
REFERENCES

1. Fossa, P. et al. *Novel angular furo and thieno-quinolinones: Synthesis and preliminary photobiological studies.* Bioorg Med Chem 2002, 10(3): 743.

PHOTODYNAMIC THERAPY

313644

3-[7(*R*)-Ethyl-2²-hexyl-12-[1-(heptyloxy)ethyl]-3,8(*R*),13,17(*S*)-tetramethyl-2¹,2³-dioxo-2¹,2²,2³,7,8,18-hexahydro-17*H*-pyrido[3,4,5-*af*]porphyrin-18(*S*)-yl]propionic acid propyl ester



C₄₉ H₆₉ N₅ O₅; Mol wt: 808.1141

ACTION – Photosensitizing agent for photodynamic therapy, a bacteriopurpurinimide with significant photosensitizing activity *in vitro* against murine fibrosarcoma RIF cells and *in vivo* in mice bearing RIF tumors, where a dose of 0.2 μ mol/kg i.v. produced complete regression of tumors in 5 of 6 animals on day 90 after treatment.

SOURCE – Health Research.

REFERENCES

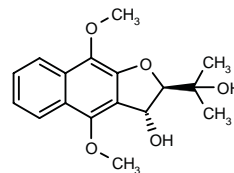
1. Pandey, R.K. et al. (Health Research, Inc.) *Long wavelength absorbing bacteriochlorin alkyl ether analogs.* EP 1164136.
2. Chen, Y. et al. *Bacteriopurpurinimides: Highly stable and potent photosensitizers for photodynamic therapy.* J Med Chem 2002, 45(2): 255.

CHEMOPREVENTIVE AGENTS

AVICENOL A

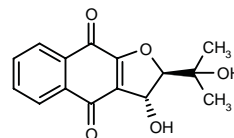
315080

(+)-2-(1-Hydroxy-1-methylethyl)-4,9-dimethoxy-2,3-dihydronaphtho[2,3-*b*]furan-3-ol



C₁₇ H₂₀ O₅; Mol wt: 304.3400

ACTION – Chemopreventive agent, a natural product isolated from *Avicennia* plants proven to inhibit Epstein-Barr virus activation induced by TPA in Raji cells, as well as tumor extension in a mouse model of skin papilloma induced by DMBA TPA. Another related compound is:



Avicequinone A [315083]: C₁₅ H₁₄ O₅

SOURCES – Kyoto Prefectural University of Medicine, Kyoto (JP); Meijo University, Nagoya (JP); National University of Singapore (SG); Tokai Gakuen University, Aichi (JP).

REFERENCES

1. Ito, C. et al. *Chemical constituents of Avicennia alba. Isolation and structural elucidation of new naphthoquinones and their analogues.* Chem Pharm Bull 2000, 48(3): 339.
2. Itoigawa, M. et al. *Cancer chemopreventive activity of naphthoquinones and their analogs from Avicennia plants.* Cancer Lett 2001, 174(2): 135.

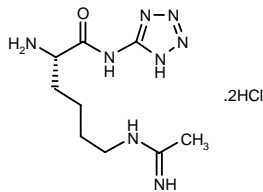
OCULAR MEDICATIONS

SC-51*

237986

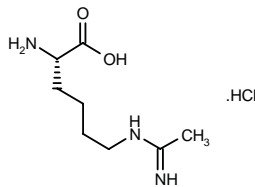
2(S)-Amino-6-(1-iminoethylamino)-N-(1H-tetrazol-5-yl)hexanamide dihydrochloride

N⁶-(1-Iminoethyl)-N¹-(1H-tetrazol-5-yl)-L-lysineamide dihydrochloride



C₉ H₁₈ N₈ O . 2HCl; Mol wt: 327.2180

ACTION – Prodrug of the potent and selective inhibitor of inducible nitric oxide synthase (iNOS, NOS-2) **L-NIL**, proven to completely prevent the loss of retinal ganglion cells in animals with chronic moderate ocular hypertension after 7 months of treatment. Delayed treatment started 3 months after induction of chronic, moderately elevated intraocular pressure was able to prevent further loss of retinal ganglion cells. Compound also exhibited chemopreventive activity in rats with colon cancer induced by azoxymethane; coadministration with the selective COX-2 inhibitor celecoxib showed additional chemopreventive activity. Potentially useful for the treatment of glaucoma and as a chemopreventive agent.



L-NIL [210831]: C₈ H₁₇ N₃ O₂ . HCl

SOURCE – Pharmacia.

REFERENCES

1. Hallinan, E.A. et al. (Pharmacia Corp.) *Aminotetrazole derivs. useful as nitric oxide synthase inhibitors*. EP 0790987, EP 1113011, JP 1998508847, US 5684008, WO 9615120.

2. Salvemini, D. (Pharmacia Corp.) *Attenuation of opioid tolerance by inhibiting inducible nitric oxide synthase pathways in the treatment of pain*. WO 9830220.

3. Hallinan, E.A. et al. *Synthesis and biological characterization of L-N⁶-(1-iminoethyl)lysine 5-tetrazole-amine, a prodrug of a selective iNOS inhibitor*. J Med Chem 2002, 45(8): 1686.

4. Neufeld, A.H. *A prodrug of a selective inhibitor of inducible nitric oxide synthase is neuroprotective in the rat model of glaucoma*. 4th Int Symp Ocular Pharmacol Pharm (Feb 28-March 3, Seville) 2002, 13.

5. Rao, C.V. et al. *Chemopreventive properties of a selective inducible nitric oxide synthase inhibitor in colon carcinogenesis, administered alone or in combination with celecoxib, a selective cyclooxygenase-2 inhibitor*. Cancer Res 2002, 62(1): 165.

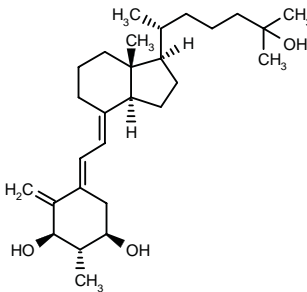
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METABOLIC DRUGS

TREATMENT OF BONE DISEASES

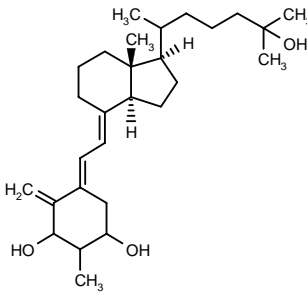
313876

(1R,2S,3R,5E,7E)-2-Methyl-9,10-secocholesta-5,7,10-triene-1,3,25-triol



C₂₈ H₄₆ O₃; Mol wt: 430.6684

ACTION – Vitamin D₃ receptor (VDR) modulator shown to inhibit the binding of 1α-25-dihydroxyvitamin D₃ to VDR. Potentially useful for the treatment of calcium metabolism disorders. Other exemplified 5,6-*trans*-alkylvitamin D derivatives are:



Compound	Isomer	Formula
313878	1S,2R,3S,20R	C ₂₈ H ₄₆ O ₃
313880	1S,2S,3S,20R	C ₂₈ H ₄₆ O ₃
313881	1R,2R,3S,20R	C ₂₈ H ₄₆ O ₃
313882	1R,2S,3S,20R	C ₂₈ H ₄₆ O ₃
313883	1R,2S,3R,20S	C ₂₈ H ₄₆ O ₃
313885	1R,2S,3S,20S	C ₂₈ H ₄₆ O ₃

SOURCE – Chugai.

REFERENCES

1. Takayama, H. and Fujishima, T. (Chugai Pharmaceutical Co. Ltd.) *5,6-trans-2-Alkylvitamin D derivs*. WO 0190061.

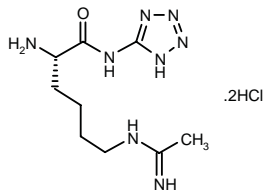
OCULAR MEDICATIONS

SC-51*

237986

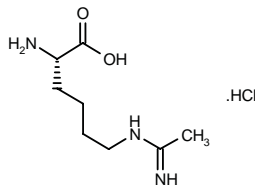
2(S)-Amino-6-(1-iminoethylamino)-N-(1H-tetrazol-5-yl)hexanamide dihydrochloride

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L-NIL [210831]: C₈ H₁₇ N₃ O₂ . HCl

SOURCE – Pharmacia.

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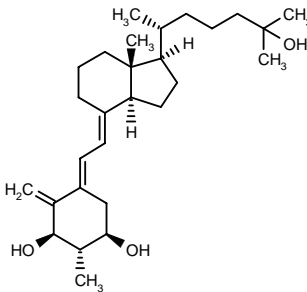
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METABOLIC DRUGS

TREATMENT OF BONE DISEASES

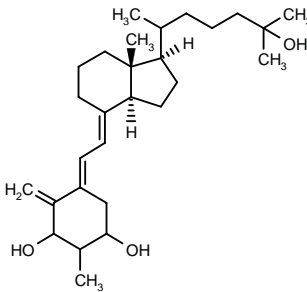
313876

(1R,2S,3R,5E,7E)-2-Methyl-9,10-secocholesta-5,7,10-triene-1,3,25-triol



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313880	1S,2S,3S,20R	C ₂₈ H ₄₆ O ₃
313881	1R,2R,3S,20R	C ₂₈ H ₄₆ O ₃
313882	1R,2S,3S,20R	C ₂₈ H ₄₆ O ₃
313883	1R,2S,3R,20S	C ₂₈ H ₄₆ O ₃
313885	1R,2S,3S,20S	C ₂₈ H ₄₆ O ₃

SOURCE – Chugai.

REFERENCES

1. Takayama, H. and Fujishima, T. (Chugai Pharmaceutical Co. Ltd.) *5,6-trans-2-Alkylvitamin D derivs*. WO 0190061.

315521

L-Alanyl-L-valyl-L-seryl-L-glutamyl-L-isoleucyl-L-glutamyl-L-leucyl-L-norleucyl-L-histidyl-L-asparaginyl-L-leucyl-glycyl-L-lysyl-L-histidyl-L-leucyl-L-asparaginyl-L-seryl-L-lysyl-L-glutamyl-L-arginyl-L-valyl-L-glutamyl-L-tryptophyl-L-leucyl-L-arginyl-L-lysyl-L-leucyl-L-leucyl-L-glutamyl-L-aspartyl-L-valinamide N-6.18-C-5.22-lactam

C164 H272 N50 O44; Mol wt: 3648.2590

ACTION – Human parathyroid hormone (PTH) analogue with an EC_{50} value of 0.097 nM for PTH receptor activation in the ROS 17/2.8 cell line. Potentially useful for the treatment of postmenopausal osteoporosis.

SOURCE – Aventis Pharma.

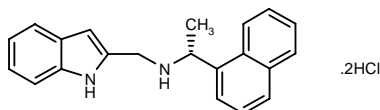
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1. Condon, S.M. and Morize, I. (Aventis Pharmaceuticals, Inc.) *Peptide parathyroid hormone analogs*. WO 9851324.

2. Condon, S.M. et al. *Analogues of human parathyroid hormone (1-31)NH2: Further evaluation of the effect of conformational constraint on biological activities*. Bioorg Med Chem 2002, 10(3): 731.

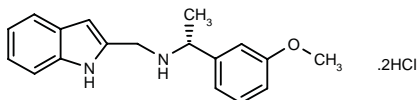
PHD-337-R**313624**

N-(1*H*-Indol-2-ylmethyl)-1(*R*)-(1-naphthyl)ethylamine dihydrochloride



C21 H20 N2 . 2HCl; Mol wt: 373.3248

ACTION – Agent with the ability to modulate calcium-sensing receptors (CaSR), as demonstrated *in vitro*, increasing the accumulation of inositol phosphates in CHO cells expressing CaSRs. Potentially useful for the treatment of disorders related to calcium imbalance such as hyperparathyroidism, osteoporosis, cancer, as well as cardiovascular, neurodegenerative, gastrointestinal and endocrine disorders. Another exemplified compound is:



PHD-356 [313625]: C18 H20 N2 O . 2HCl

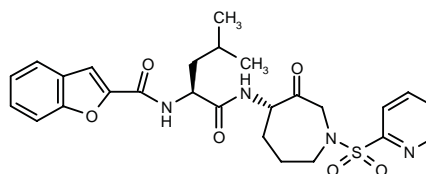
SOURCE – CNRS.

REFERENCES

1. Ruat, M. et al. (CNRS [Centre National de la Recherche Scientifique]) *Novel calcium receptor active molecules and method for preparing same*. FR 2809396, WO 0190069.

SB-357114***302658**

N-[3-Methyl-1(*S*)-[N-[3-oxo-1-(pyridin-2-ylsulfonyl)-perhydroazepin-4(*S*)-yl]carbamoyl]butyl]-1-benzofuran-2-carboxamide



C26 H30 N4 O6 S; Mol wt: 526.6110

ACTION – Cathepsin K inhibitor (K_i = 0.16 nM) with high selectivity versus cathepsin B (K_i = 500 nM) and some selectivity relative to cathepsin L and S (K_i = 2.2 and 4.0 nM, respectively). The compound strongly inhibited human osteoclast-mediated bone resorption (IC_{50} = 29-70 nM). In ovariectomized cynomolgus monkeys, a dose of 12 mg/kg s.c. once daily for 5 days produced significant reductions in markers of bone resorption and turnover even after the first dose. Potentially useful for the treatment of postmenopausal osteoporosis.

SOURCE – GlaxoSmithKline.

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2. Marquis, R.W. Jr. et al. (GlaxoSmithKline Inc.) *Protease inhibitors*. EP 1158986, WO 0038687.

3. Marquis, R.W. Jr. et al. (GlaxoSmithKline Inc.) *Protease inhibitors*. WO 0195911.

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5. Stroup, G.B. et al. *Inhibition of cathepsin K by SB 357114 results in inhibition of bone resorption in vitro and in vivo in non-human primates*. 22nd Annu Meet Am Soc Bone Miner Res (ASBMR) (Sept 22-26, Toronto) 2000, Abst 1162.

6. Stroup, G.B. et al. *Potent and selective inhibition of human cathepsin K leads to inhibition of bone resorption in vivo in a nonhuman primate*. J Bone Miner Res 2001, 16(10): 1739.

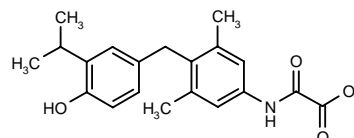
7. Zaidi, M. et al. *Cathepsin K, osteoclastic resorption, and osteoporosis therapy*. J Bone Miner Res 2001, 16(10): 1747.

*Identified compound **302658** Drug Data Rep 2001, 023(07): 0721.

TREATMENT OF LIPOPROTEIN DISORDERS

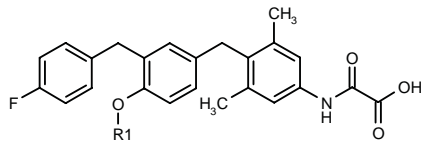
313618

N-[4-(4-Hydroxy-3-isopropylbenzyl)-3,5-dimethylphenyl]-oxamic acid



C20 H23 N O4; Mol wt: 341.4047

ACTION – Thyroid hormone receptor agonist that induced luciferase activity in HepG2 cells transfected with the luciferase gene under the control of a thyroid hormone-regulated promoter ($EC_{50} = 0.14 \text{ nM}$), thus proving its thyroid-like profile. Potentially useful in the treatment of arteriosclerosis and hypercholesterolemia. Other exemplified 1,1-diphenylmethane derivatives are:



Compound	R1	Formula
313619	H	C ₂₄ H ₂₂ FNO ₄
313621	Me	C ₂₅ H ₂₄ FNO ₄

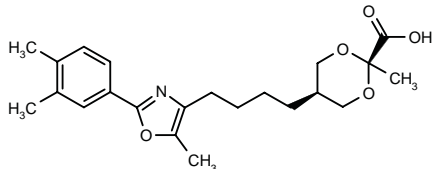
SOURCE – Bayer.

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1. Haning, H. et al. (Bayer AG) *Diphenylmethane derivs.* DE 10024939, WO 0190053.

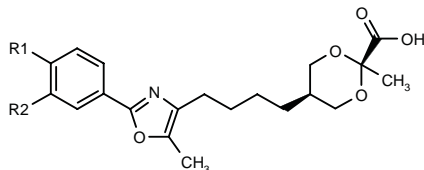
313985

cis-5-[4-[2-(3,4-Dimethylphenyl)-5-methyloxazol-4-yl]-butyl]-2-methyl-1,3-dioxane-2-carboxylic acid



C22 H29 N O5; Mol wt: 387.4731

ACTION – Agent with the ability to decrease blood levels of triglycerides, LDL cholesterol and glucose, and thus potentially useful for the treatment of cardiovascular diseases, cerebral infarction, hyperlipidemia, arterio-sclerosis, diabetes, hypertension, obesity, etc. This compound decreased blood levels of glucose (53%), triglycerides (92%) and insulin (68%) when administered orally to mice at 3 mg/kg. This compound was also able to decrease LDL cholesterol serum levels, thus providing protection against arteriosclerosis. Other exemplified heterocyclic compounds are:



Compound	R1	R2	Formula
313986	Me	H	C ₂₁ H ₂₇ NO ₅
313987	H	Me	C ₂₁ H ₂₇ NO ₅

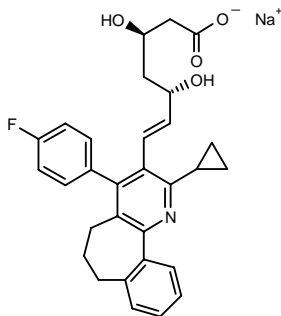
SOURCE – Nippon Shinyaku.

REFERENCES

1. Kuwabara, K. and Aoki, T. (Nippon Shinyaku Co., Ltd.) *Heterocyclic cpds.* WO 0190087.

314403

7-[2-Cyclopropyl-4-(4-fluorophenyl)-6,7-dihydro-5H-benzo[6,7]cyclohepta[1,2-*b*]pyridin-3-yl]-3(*R*),5(*S*)-dihydroxy-6(*E*)-heptenoic acid sodium salt



C30 H29 F N Na O4; Mol wt: 509.5501

ACTION – HMG-CoA reductase inhibitor reported to lower LDL cholesterol and/or increase HDL cholesterol, and therefore potentially useful for the treatment of lipid metabolism disorders and atherosclerosis.

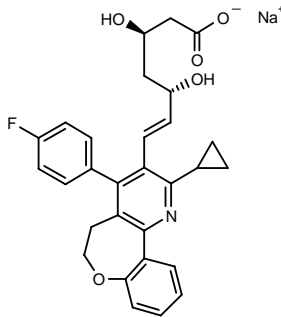
SOURCE – Bristol-Myers Squibb.

REFERENCES

1. Robl, J.A. et al. (Bristol-Myers Squibb Co.) *HMG-CoA reductase inhibitors and method.* WO 0196311.

314404

7-[2-Cyclopropyl-4-(4-fluorophenyl)-5,6-dihydro[1]-benzoxepino[5,4-*b*]pyridin-3-yl]-3(*R*),5(*S*)-dihydroxy-6-heptenoic acid sodium salt



C29 H27 F N Na O5; Mol wt: 511.5223

ACTION – HMG-CoA reductase inhibitor reported to lower LDL cholesterol and/or increase HDL cholesterol, and therefore potentially useful for the treatment of lipid metabolism disorders and atherosclerosis.

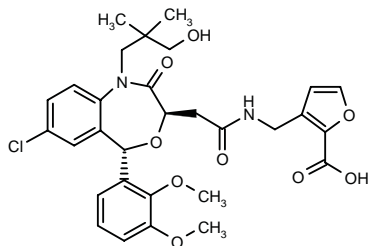
SOURCE – Bristol-Myers Squibb.

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1. Robl, J.A. et al. (Bristol-Myers Squibb Co.) *HMG-CoA reductase inhibitors and method.* WO 0196347.

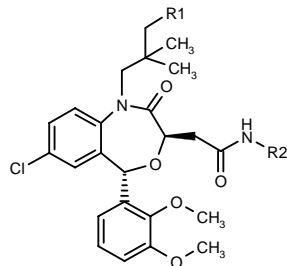
314796

3-[2-[7-Chloro-5(*S*)-(2,3-dimethoxyphenyl)-1-(3-hydroxy-2,2-dimethylpropyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3(*R*)-yl]acetamidomethyl]furan-2-carboxylic acid



C30 H33 Cl N2 O9; Mol wt: 601.0487

ACTION – Squalene synthase inhibitor with an IC₅₀ of 9.1 nM against squalene synthase from human hepatic cancer HepG2 cells. Potentially useful for the treatment of hyperlipidemia. Other exemplified benzoxazepinones are:



Compound	R1	R2	Formula
314798	OH	SO2Pr	C ₂₇ H ₃₅ ClN ₂ O ₈ S
314804	H	(<i>R</i>)-CH(Me)CO2H	C ₂₇ H ₃₃ ClN ₂ O ₇
314806	OH	trans-4-CO2H-cyclohexyl-CH2	C ₃₂ H ₄₁ ClN ₂ O ₈
314807	OAce	trans-4-CO2H-cyclohexyl-CH2	C ₃₄ H ₄₃ ClN ₂ O ₉
314808	OH	3-CO2H-2-furyl-CH2CH2	C ₃₁ H ₃₅ ClN ₂ O ₉
314809	OH	3-(CO2HCH2CH2)-Ph	C ₃₃ H ₃₇ ClN ₂ O ₈
314810	OH	2-MeO-5-(CO2HCH2CH2)-Ph	C ₃₄ H ₃₉ ClN ₂ O ₉
314812	OH	2-F-5-(CO2HCH2CH2)-Ph	C ₃₃ H ₃₆ ClFN ₂ O ₈
314813	OH	2-Me-5-(CO2HCH2CH2)-Ph	C ₃₄ H ₃₉ ClN ₂ O ₈
314814	H	3-(CO2HCH2CH2)-Ph	C ₃₃ H ₃₇ ClN ₂ O ₇
314817	OH	4-(CO2HCH2)-PhCH2	C ₃₃ H ₃₇ ClN ₂ O ₈
314818	OH	3-(CO2HCH2CH2)-PhCH2	C ₃₄ H ₃₉ ClN ₂ O ₈

SOURCE – Takeda.

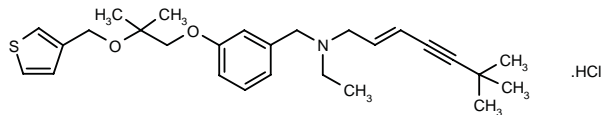
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1. Kori, M. et al. (Takeda Chemical Industries, Ltd.) *Benzoxazepinones and their use as squalene synthase inhibitors*. WO 0198282.

FR-194738*

263357

(*E*)-*N*-(6,6-Dimethylhept-2-en-4-ynyl)-*N*-ethyl-*N*-[3-[2-methyl-2-(thien-3-ylmethoxy)propoxy]benzyl]amine hydrochloride



C27 H37 N O2 S . HCl; Mol wt: 476.1212

ACTION – Hypolipidemic agent, a potent inhibitor of hepatic squalene epoxidase (squalene monooxygenase; IC₅₀ = 9.8 nM in HepG2 cells) able to inhibit cholesterol synthesis (IC₅₀ = 4.9 nM) and to induce intracellular [¹⁴C]-squalene accumulation in intact HepG2 cells. Unlike simvastatin, compound only moderately (4.6-fold) upregulates HMG-CoA reductase activity at the highest concentration tested of 1000 nM, which inhibited cholesterol synthesis by 90%.

SOURCE – Fujisawa.

REFERENCES

1. Okumura, H. et al. (Fujisawa Pharmaceutical Co., Ltd.) *Substd. amine derivs*. JP 2000517314, WO 9808838.

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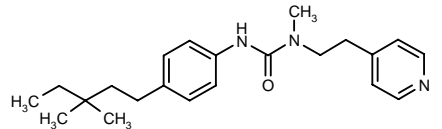
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*Identified compound **263357** Drug Data Rep 1998, 020(07): 0639.

TREATMENT OF OBESITY AND NUTRITIONAL DISORDERS

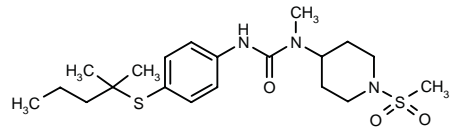
313657

N-[4-(3,3-Dimethylpentyl)phenyl]-*N*'-methyl-*N*'-[2-(4-pyridyl)ethyl]urea



C22 H31 N3 O; Mol wt: 353.5069

ACTION – An antagonist of neuropeptide Y (NPY) Y₅ receptors with a K_i of 0.4 nM at Y₅ receptors expressed in CHO cells. Potentially useful for the treatment of eating disorders and diabetes. Another compound within this series of urea derivatives is:



313659: C20 H33 N3 O3 S2

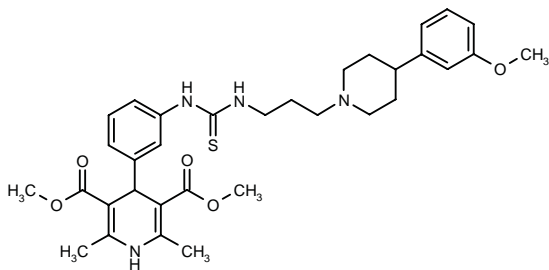
SOURCE – Schering-Plough.

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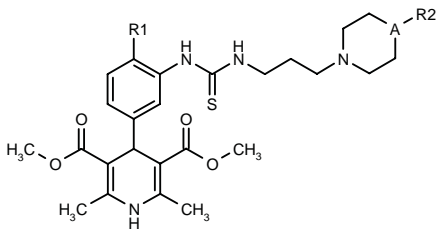
313689

4-[3-[3-[3-[4-(3-Methoxyphenyl)piperidin-1-yl]propyl]-thioureido]phenyl]-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylic acid dimethyl diester



C33 H42 N4 O5 S; Mol wt: 606.7838

ACTION – Neuropeptide Y (NPY) Y₁ antagonist, potentially useful for promoting weight loss and treating eating disorders. Other specifically claimed thiourea derivatives include the following:



Compound	R1	R2	A	Formula
313692	H	Ph	CH	C ₃₂ H ₄₀ N ₄ O ₄ S
313693	F	Ph	CH	C ₃₂ H ₃₉ FN ₄ O ₄ S
313694	F	Me	CH	C ₂₇ H ₃₇ FN ₄ O ₄ S
313695	F	Et	CH	C ₂₈ H ₃₉ FN ₄ O ₄ S
313696	F	Pr	CH	C ₂₉ H ₄₁ FN ₄ O ₄ S
313697	F	t-Bu	CH	C ₃₀ H ₄₃ FN ₄ O ₄ S
313698	F	i-Pr	CH	C ₂₉ H ₄₁ FN ₄ O ₄ S
313699	F	cyclohexyl	N	C ₃₁ H ₄₄ FN ₅ O ₄ S

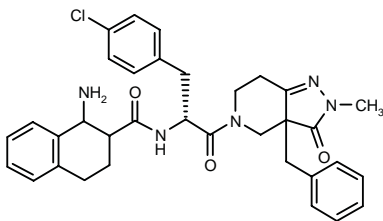
SOURCE – Bristol-Myers Squibb.

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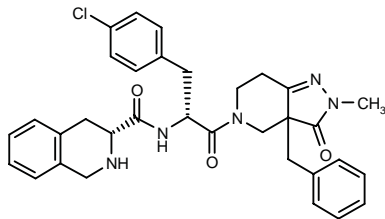
313941

1-Amino-N-[2-(3a-benzyl-2-methyl-3-oxo-3,3a,4,5,6,7-hexahydro-2H-pyrazolo[4,3-c]pyridin-5-yl)-1(R)-(4-chlorobenzyl)-2-oxoethyl]-1,2,3,4-tetrahydronaphthalene-2-carboxamide



C34 H36 Cl N5 O3; Mol wt: 598.1434

ACTION – Selective melanocortin MC₄ receptor agonist, potentially useful in the treatment of obesity, diabetes and male or female sexual disorders including erectile dysfunction. Another specifically claimed compound is:



313945: C33 H34 Cl N5 O3

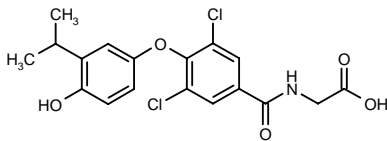
SOURCE – Merck & Co.

REFERENCES

1. Bakshi, R.K. et al. (Merck & Co., Inc.) *Melanocortin receptor agonists*. WO 0191752.

314241

N-[3,5-Dichloro-4-(4-hydroxy-3-isopropylphenoxy)-benzoyl]glycine



C18 H17 Cl2 N O5; Mol wt: 398.2403

ACTION – Agent that acts as a thyroid hormone receptor β ligand, potentially useful for the treatment of obesity, hypercholesterolemia, atherosclerosis, depression, osteoporosis, hypothyroidism, goiter, thyroid cancer, glaucoma, cardiac arrhythmia, congestive heart failure and skin disorders.

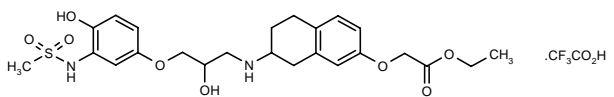
SOURCE – Bristol-Myers Squibb.

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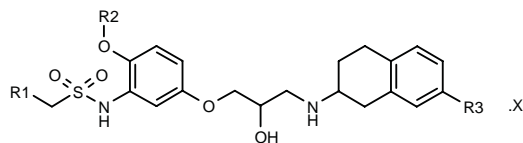
314303

2-[7-[2-Hydroxy-3-[4-hydroxy-3-(methylsulfonamido)-phenoxy]propylamino]-5,6,7,8-tetrahydronaphthalen-2-yloxy]acetic acid ethyl ester trifluoroacetate



C24 H32 N2 O8 S . C2 H F3 O2; Mol wt: 622.6107

ACTION – A β_3 -adrenoceptor agonist considered to have potential in the treatment of obesity, diabetes, irritable bowel syndrome, urinary incontinence and pollakiuria, among other conditions. Other exemplified propanol-amino-tetralins are:



Compound	R1	R2	R3	Isomer	X	Formula
314304	H	H	OCH2CO2Et	S,S	H2O	C ₂₄ H ₃₂ N ₂ O ₆ S .H ₂ O
314305	H	H	1-Pip-COCH2O			C ₂₇ H ₃₇ N ₃ O ₇ S
314306	H	H	1-Pip-COCH2O	S,S		C ₂₇ H ₃₇ N ₃ O ₇ S
314307	H	H	OCH2CONH2	S,S		C ₂₂ H ₂₉ N ₃ O ₇ S
314308	H	H	OCH2CON(Et)2	S,S		C ₂₆ H ₃₇ N ₃ O ₇ S
314309	H	H	OCH2CONHBu	S,S		C ₂₆ H ₃₇ N ₃ O ₇ S
314310	H	H	OCH2CO-NHCH2Ph	S,S		C ₂₉ H ₃₅ N ₃ O ₇ S
314311	Et	H	OCH2CO2Et	S,S		C ₂₆ H ₃₆ N ₂ O ₆ S
314322	H	H	1-Pip-CO-CH2CH2	S,S		C ₂₈ H ₃₉ N ₃ O ₆ S
314323	H	H	CH2CH2CO2Et	S,S		C ₂₅ H ₃₄ N ₂ O ₇ S
314324	H	CH2Ph	OCH2CO2H	S,S	CF3CO2H	C ₂₉ H ₃₄ N ₂ O ₈ S .C ₂ HF ₃ O ₂

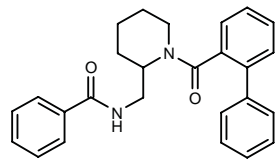
SOURCE – Sanofi-Synthélabo.

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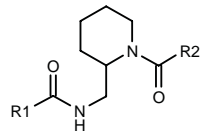
314499

N-[1-(Biphenyl-2-ylcarbonyl)piperidin-2-ylmethyl]benzamide



C26 H26 N2 O2; Mol wt: 398.5034

ACTION – Orexin-1 receptor antagonist, potentially useful for the treatment of obesity such as that associated with type 2 diabetes, as well as sleep disorders. Other exemplified aromatic carboxamides include the following:



Compound	R1	R2	Isomer	Formula
314507	2-Pyr	2-Me-5-Ph-4-thiazolyl		C ₂₃ H ₂₄ N ₄ O ₂ S
314508	4-F-Ph	2-Ph-Ph	S	C ₂₆ H ₂₅ FN ₂ O ₂
314509	4-quinolyl	2-Me-5-Ph-4-thiazolyl	S	C ₂₇ H ₂₆ N ₄ O ₂ S
314510	7-benzofuryl	2-Me-5-Ph-4-thiazolyl	S	C ₂₈ H ₂₅ N ₃ O ₃ S
314512	2-pyrazinyl	2-Me-5-(4-F-Ph)-4-thiazolyl	S	C ₂₂ H ₂₂ FN ₅ O ₂ S
314513	4-F-Ph	5-Ph-4-thiazolyl	S	C ₂₃ H ₂₂ FN ₃ O ₂ S
314515	4-F-Ph	3-(2-Cl-Ph)-5-Me-4-isoxazolyl	S	C ₂₄ H ₂₃ ClFN ₃ O ₃
314516	3,4-(F)2-Ph	2-(2-pyrimidinyl)-3-thienyl	S	C ₂₂ H ₂₀ F ₂ N ₄ O ₂ S
314519	3,4-(F)2-Ph	2-(CH2OH)-5-(4-F-Ph)-4-thiazolyl	S	C ₂₄ H ₂₂ F ₃ N ₃ O ₃ S

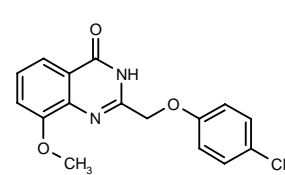
SOURCE – GlaxoSmithKline.

REFERENCES

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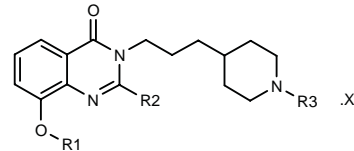
314593

2-(4-Chlorophenoxy)methyl-8-methoxyquinazolin-4(3H)-one

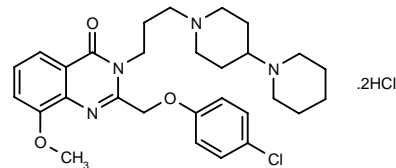


C16 H13 Cl N2 O3; Mol wt: 316.7427

ACTION – Neuropeptide Y (NPY) antagonist with potential for the treatment of eating disorders such as obesity and bulimia, cardiovascular disorders including heart failure, hypertension, angina pectoris, myocardial infarction and arrhythmia, renal conditions, CNS disorders such as stroke, neurodegeneration and epilepsy, schizophrenia, dementia, pain, abnormal gastrointestinal motility, asthma and abnormal hormone release. Other exemplified quinazoline derivatives include the following:



Compound	R1	R2	R3	X	Formula
314594	Me	4-Cl-PhOCH2	H	HCl	C ₂₄ H ₂₈ ClN ₃ O ₃ .HCl
314595	Me	4-Cl-PhOCH2	1-Pip-(CH2)3		C ₃₂ H ₄₃ ClN ₄ O ₃
314597	Me	4-Cl-PhCH=CH	1-Pip-(CH2)3		C ₃₃ H ₄₃ ClN ₄ O ₂
314598	Me	5-Me-1,3,4-thia-diazol-2-yl-SCH2	H		C ₂₁ H ₂₇ N ₅ O ₂ S ₂
314599	1-Pip-(CH2)3	4-Cl-PhCH=CH	PhCH2CH2		C ₄₀ H ₄₉ ClN ₄ O ₂



314596: C29 H37 Cl N4 O3 . 2HCl

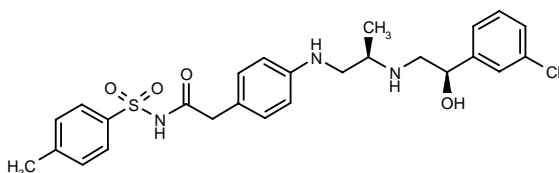
SOURCE – Pfizer.

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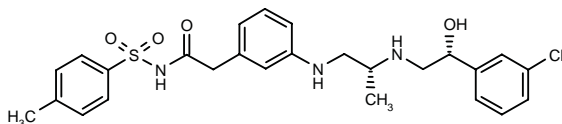
314654

N-[2-[4-[2(*R*)-[2(*R*)-(3-Chlorophenyl)-2-hydroxyethyl-amino]propylamino]phenyl]acetyl]-4-methylbenzenesulfonamide



C₂₆ H₃₀ Cl N₃ O₄ S; Mol wt: 516.0590

ACTION – Potent and selective β_3 -adrenoceptor agonist (pEC_{50} = 8.9 for stimulation of cAMP accumulation in CHO cells expressing human β_3 -adrenoceptors) with 63- and 501-fold selectivity over β_2 - and β_1 -adrenoceptors, respectively. Compound showed moderately low plasma clearance in dogs and measurable plasma levels at 2.5 h following an i.v. dose of 0.2 mg/kg. In mice, doses of 0.1-1 mg/kg p.o. produced a significant increase in thermogenesis, the effect of the higher dose lasting for up to 4 h. Potentially useful for the treatment of obesity and type 2 diabetes. Another acylsulfonamide is:



314656: C₂₆ H₃₀ Cl N₃ O₄ S

SOURCE – GlaxoSmithKline.

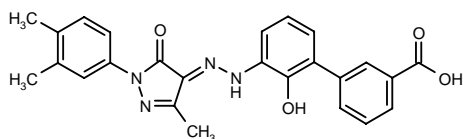
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HEMATINIC AGENTS AND HEMATOPOIETIC GROWTH FACTORS

313630

3'-[2-[1-(3,4-Dimethylphenyl)-3-methyl-5-oxo-4,5-dihydro-1*H*-pyrazol-4-ylidene]hydrazino]-2'-hydroxybiphenyl-3-carboxylic acid



C₂₅ H₂₂ N₄ O₄; Mol wt: 442.4728

ACTION – Thrombopoietin (TPO) mimetic that gave an EC_{50} of 0.03 μ M (100% of maximal TPO effect) in a proliferation assay using the TPO-dependent UT7TPO cell line. Potentially useful for the treatment of thrombocytopenia and other disorders associated with depressed platelet production.

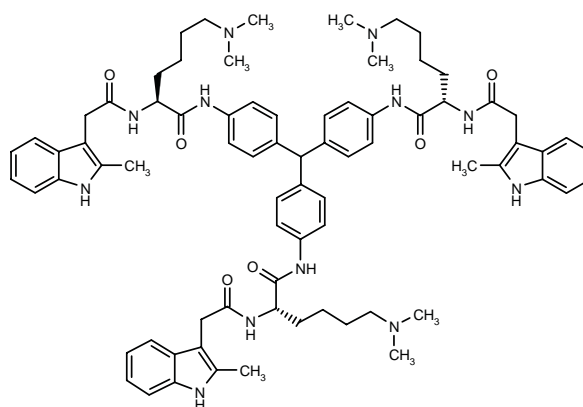
SOURCE – GlaxoSmithKline.

REFERENCES

1. Duffy, K.J. et al. (GlaxoSmithKline plc) *Thrombopoietin mimetics.* WO 0189457.

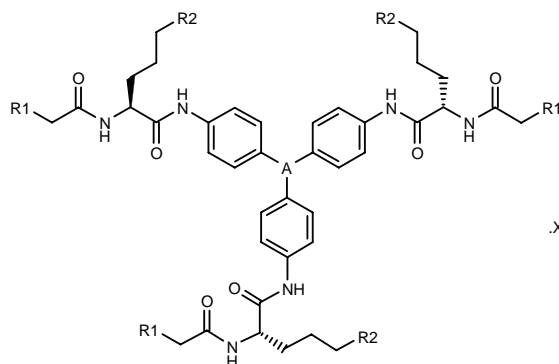
313988

*N*¹,*N*^{1'},*N*^{1''}-Methylidinetris(1,4-phenylene)tris[*N*⁶,*N*⁶-dimethyl-*N*²-[2-(2-methyl-1*H*-indol-3-yl)acetyl]-L-lysine]



C₇₆ H₉₄ N₁₂ O₆; Mol wt: 1271.6570

ACTION – Agent with thrombopoietin-like activity proven to exert a platelet-increasing effect with low antigenicity. Potentially useful for the treatment of thrombocytopenia. Other exemplified compounds are:



Compound	R1	R2	A	X	Formula
313990	3-thienyl	NHC(=NH)NH ₂	CH	HCl	C ₅₅ H ₆₇ N ₁₅ O ₆ S ₃ ·HCl
313991	3-indolyl	CH ₂ NH ₂	N	CF ₃ CO ₂ H	C ₆₆ H ₇₅ N ₁₃ O ₆ ·C ₂ HF ₃ O ₂

SOURCE – Chugai.

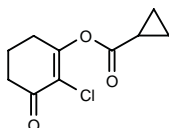
REFERENCES

1. Fujiwara, S. et al. (Chugai Pharmaceutical Co. Ltd.) *Cpds. exhibiting thrombopoietin-like activities.* WO 0192211.

THERAPY OF INBORN ERRORS OF METABOLISM

315505

Cyclopropanecarboxylic acid 2-chloro-3-oxo-1-cyclohexen-1-yl ester



C10 H11 Cl O3; Mol wt: 214.6469

ACTION – 4-Hydroxyphenylpyruvate dioxygenase inhibitor (IC_{50} = 0.015 μ M against pig liver enzyme), potentially useful for the treatment of the fatal hereditary disease tyrosinemia type I.

SOURCE – Tunghai University, Taichung (TW).

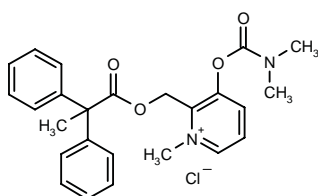
REFERENCES

1. Lin, Y.-L. et al. *SAR studies of 3-cyclopropanecarboxyloxy-2-cyclohexen-1-one as inhibitors of 4-hydroxyphenylpyruvate dioxygenase*. *Bioorg Med Chem* 2002, 10(3): 685.

TREATMENT OF POISONING, DRUG ABUSE AND DEPENDENCY

315013

3-(Dimethylaminocarbonyloxy)-2-(2,2-diphenylpropionyl)-oxymethyl)-1-methylpyridinium chloride



C25 H27 Cl N2 O4; Mol wt: 454.9513

ACTION – Pyridostigmine-aprophen prodrug proven to inhibit both acetylcholinesterase and butyrylcholinesterase (K_i = 5.62 and 3.14 μ M, respectively) and showing a competitive antagonist effect at muscarinic receptors (K_i = 4.7 μ M). Potentially useful for the prophylaxis and therapy of organophosphate poisoning.

SOURCE – Walter Reed Army Institute, Washington, DC (US).

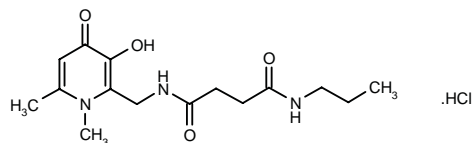
REFERENCES

1. Leader, H. et al. *Pyridophens: Binary pyridostigmine-aprophen prodrugs with differential inhibition of acetylcholinesterase, butyrylcholinesterase, and muscarinic receptors*. *J Med Chem* 2002, 45(4): 902.

CP-358

314662

*N*¹-(3-Hydroxy-1,6-dimethyl-4-oxo-1,4-dihydropyridin-2-ylmethyl)-*N*⁴-propylsuccinamide hydrochloride



C15 H23 N3 O4 . HCl; Mol wt: 345.8246

ACTION – Iron chelator with *in vivo* iron-scavenging activity in ⁵⁹Fe-ferritin-loaded rats (23.3% iron mobilization at 450 μ mol/kg p.o.). Compound also showed weak inhibitory activity against 5-lipoxygenase *in vitro*. Potentially useful for the treatment of iron overload.

SOURCES – King's College London, London (GB); University College London, London (GB).

REFERENCES

1. Kayyali, R. et al. *Structure-function investigation of the interaction of 1- and 2-substituted 3-hydroxypyridin-4-ones with 5-lipoxygenase and ribonucleotide reductase*. *J Biol Chem* 2001, 276(52): 48814.
2. Liu, Z.D. et al. *Design, synthesis, and evaluation of novel 2-substituted 3-hydroxypyridin-4-ones: Structure-activity investigation of metalloenzyme inhibition by iron chelators*. *J Med Chem* 2002, 45(3): 631.

DIGOXIN IMMUNE FAB (OVINE)

258498

ACTION – Digoxin immune ovine Fab immunoglobulin fragments that bind to digoxin and reduce free digoxin levels.

INDICATION – Treatment of patients with life-threatening or potentially life-threatening digoxin toxicity or overdose.

PRESENTATION – Vials, 40 mg digoxin immune Fab which will bind approximately 0.5 mg digoxin.

PROPRIETARY NAME – *DigiFab* (US).

SOURCES – Protherics; marketed by Savage Laboratories (Altana).

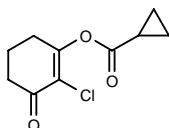
REFERENCES

1. *Clinical trial results show DigiTAB to be safe and effective for oleander poisoning*. *DailyDrugNews.com* (Daily Essentials) 2000, March 28.
2. *FDA accepts DigiTAB filing for review*. *DailyDrugNews.com* (Daily Essentials) 1999, Oct 15.
3. *New treatment for digoxin toxicity or overdose available in the U.S.* *DailyDrugNews.com* (Daily Essentials) 2002, March 11.
4. *Protherics provides interim update on product development*. *DailyDrugNews.com* (Daily Essentials) 2001, Jan 12.
5. *Protherics updates programs, announces collaboration with Lilly*. *DailyDrugNews.com* (Daily Essentials) 1999, Dec 23.
6. *Therapeutic Antibodies and Altana enter alliance for emergency medicine products*. *DailyDrugNews.com* (Daily Essentials) 1997, Oct 17.
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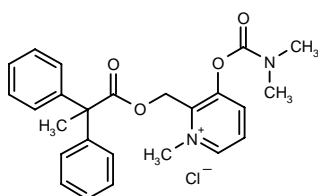
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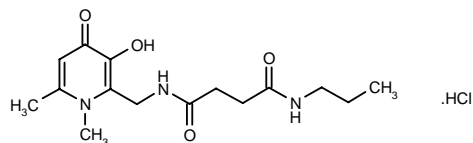
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CP-358

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10. *Therapeutic Antibodies: Q1 1998 highlights*. DailyDrugNews.com (Daily Essentials) 1998, May 29.

11. *Therapeutic Antibodies: Q3 1997 highlights*. DailyDrugNews.com (Daily Essentials) 1997, Dec 5.

12. *Therapeutic Antibodies: year-end 1998 highlights*. DailyDrugNews.com (Daily Essentials) 1999, April 27.

DIAGNOSTIC AGENTS

315078

L-Tyr-L-Ala-L-Ala-L-Gln-L-Asn-L-Arg-L-Arg-Gly-L-Leu-L-Asp-L-Leu-L-Leu-L-Phe-L-Trp-L-Glu-L-Gln-Gly-Gly-L-Leu-L-Cys-L-Lys-L-Ala-L-Leu-L-Gln-L-Glu-L-Gln-L-Cys-Gly-Gly-L-Leu-L-Leu-L-Pro-L-His-L-Ser-L-Asn-L-Leu-L-Asp-L-His-L-Ile-L-Leu-L-Glu-L-Pro-L-Ser-L-Ile-L-Phe-L-Trp-L-Lys-OH

C243 H371 N67 O67 S2; Mol wt: 5367.1380

ACTION – Diagnostic agent for human T-cell lymphotropic virus type I (HTLV-I), a synthetic chimeric peptide incorporating sequences from envelope gp46 and transmembrane gp21 glycoproteins, with high sensitivity and specificity for detecting antibody in sera from infected patients.

SOURCES – Center for Genetic Engineering and Biotechnology, Havana (CU); Immunoassay Center, Havana (CU).

REFERENCES

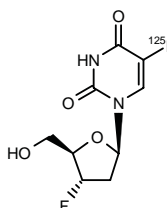
1. Marin, M.H. et al. *Chimeric synthetic peptides containing two immunodominant epitopes from the envelope gp46 and the transmembrane gp21 glycoproteins of HTLV-I virus*. Biochem Biophys Res Commun 2001, 289(1): 1.

[¹²⁵I]-DRE-368

314618

1-(2,3-Dideoxy-3-fluoro-β-D-ribofuranosyl)-5-[¹²⁵I]iodouracil

2',3'-Dideoxy-3'-fluoro-5-[¹²⁵I]iodouridine



C9 H10 F I N2 O4; Mol wt: 354.1860

ACTION – A radiolabeled nucleoside compound for use as an imaging or therapeutic agent in the field of cancer. Compound was stable in rat plasma *in vitro* and in dog plasma *in vivo*, and it demonstrated time- and concentration-dependent uptake by human colon adenocarcinoma LS 180 cells. Pharmacokinetic studies in mice bearing LS 180 xenografts showed increasing concentrations of [¹²⁵I]-DRE-368 over time in tumor, stomach and thyroid gland following i.v. administration. This route of administration allowed clear tumor imaging 30 min after a dose of 37 MBq.

SOURCE – Daiichi Radioisotope.

REFERENCES

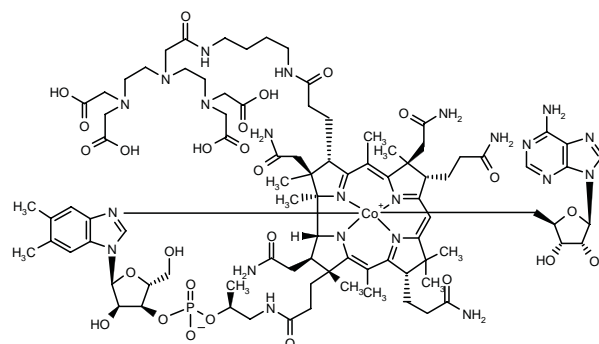
1. Namioka, H. et al. (Daiichi Radioisotope Labs., Ltd.) *Radioactive nucleoside cpds. and medicines containing them*. JP 2001328997.

DTPA-ADENOSYLCOBALAMIN

314053

N^b-[4-[2-[*N,N*-Bis[2-[*N,N*-bis(carboxymethyl)amino]ethyl]amino]acetamido]butyl]-Co-(5'-deoxyadenosin-5'-yl)cobinamide *f*-(dihydrogen phosphate) inner salt 3'-ester with [5,6-dimethyl-1-(α-D-ribofuranosyl)benzimidazole-κ^N3]

DAC



C90 H130 Co N22 O26 P; Mol wt: 2026.0520

ACTION – Analogue of vitamin B₁₂ that is potentially useful for the diagnosis of breast and lung cancer when radiolabeled with indium 111. Preclinical studies in sarcoma-bearing mice demonstrated that 24 h after administration, the uptake of the radiolabeled complex into transplanted sarcomas was 2-4-fold higher than in liver, spleen and pancreas, and 20-29-fold higher than in heart, lung, fat and muscle. A study in patients with previously diagnosed cancer including breast, lung, colon, thyroid, bone, prostate and brain cancer and lymphoma demonstrated that the vitamin B₁₂ analogue was taken up in malignant tissue following administration of radiolabeled complex and that it located cancers in early stages. The most promising results were seen in breast cancer, where the complex confirmed the presence of cancer in 8 of 9 patients including 1 whose cancer was missed by physical exam, mammography and ultrasound. The efficacy of the agent was not affected by tissue density.

SOURCES – Copharos; Mayo Foundation, Rochester, MN (US); University of Minnesota, Minneapolis, MN (US).

8. *Therapeutic Antibodies submits PLA and ELA for DigiTab*. DailyDrugNews.com (Daily Essentials) 1999, Aug 12.

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315078

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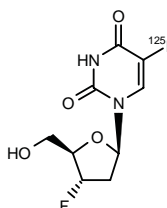
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SOURCE – Daiichi Radioisotope.

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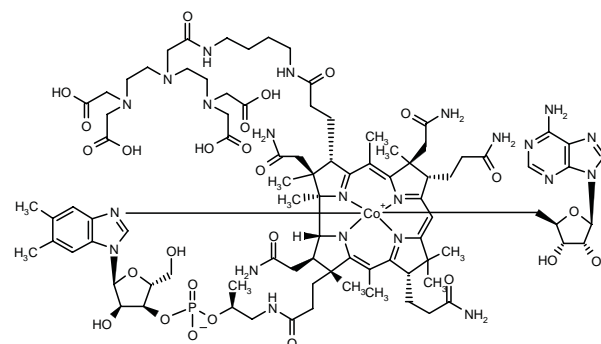
1. Namioka, H. et al. (Daiichi Radioisotope Labs., Ltd.) *Radioactive nucleoside cpds. and medicines containing them*. JP 2001328997.

DTPA-ADENOSYLCOBALAMIN

314053

N^b-[4-[2-[*N,N*-Bis[2-[*N,N*-bis(carboxymethyl)amino]ethyl]amino]acetamido]butyl]-Co-(5'-deoxyadenosin-5'-yl)cobinamide *f*-(dihydrogen phosphate) inner salt 3'-ester with [5,6-dimethyl-1-(α-D-ribofuranosyl)benzimidazole-κ^N3]

DAC



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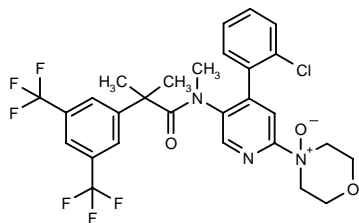
1. Collins, D.A. and Hogenkamp, H.P.C. (Mayo Foundation for Medical Education and Research;University of Minnesota) *Radionuclide labeling of vitamin B12 and coenzymes thereof*. WO 9718231.
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3. Collins, D.A. and Hogenkamp, H.P.C. *Transcobalamin II receptor imaging via radiolabeled diethylene-triaminepentaacetate cobalamin analogs*. J Nucl Med 1997, 38(5): 717.
4. Douglas, A. et al. *Biodistribution of radiolabeled adenosylcobalamin in patients diagnosed with various malignancies*. Mayo Clin Proc 2000, 75(6): 568.
5. Douglas, A. et al. *Tumor imaging via indium 111-labeled DTPA-adenosylcobalamin*. Mayo Clin Proc 1999, 74(7): 687.
6. Frohlich, D.E.C. et al. *Radionuclide imaging of human breast carcinoma cell line MDA-MB-231 via In-111 DTPA-adenosylcobalamin, In 111 DTPA-octreotide, GA-67 citrate, and Tl-201 chloride*. 23rd Annu San Antonio Breast Cancer Symp (Dec 6-9, San Antonio) 2000, Abst 508.
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ANALGESIC AND ANESTHETIC
DRUGS

ANALGESIC DRUGS

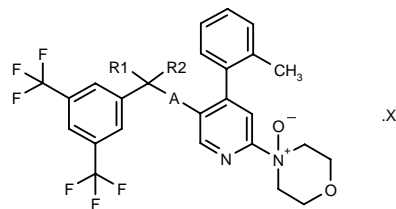
316098

2-[3,5-Bis(trifluoromethyl)phenyl]-N-[4-(2-chlorophenyl)-6-(4-oxidomorpholin-4-yl)pyridin-3-yl]-N,2-dimethyl-propionamide



C28 H26 Cl F6 N3 O3; Mol wt: 601.9724

ACTION – Tachykinin NK₁ receptor antagonist (pK_i = 8.3-8.7) prodrug with potential in the treatment of pain, migraine, Alzheimer's disease, multiple sclerosis, morphine withdrawal, edema, rheumatoid arthritis, asthma, bronchial hyperreactivity, allergic rhinitis, ulcerative colitis, Crohn's disease, ocular injury, ocular inflammatory diseases and motion sickness, among other conditions. Other exemplified compounds are:



Compound	R1=R2	A	X	Formula
316103	Me	-CON(Me)-		C ₂₉ H ₂₉ F ₆ N ₃ O ₃
316104	H	-N(Me)CO-	H ₂ O	C ₂₇ H ₂₅ F ₆ N ₃ O ₃ ·H ₂ O

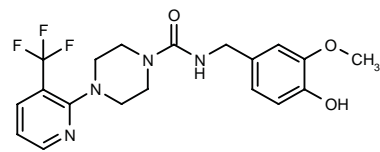
SOURCE – Roche.

REFERENCES

1. Hoffmann, T. et al. (F. Hoffmann-La Roche AG) *N*-Oxides as NK₁ receptor antagonist prodrugs of 4-phenyl-pyridine derivs.. WO 0206236.

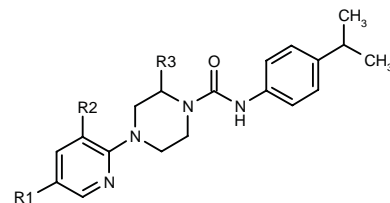
316545

N-(4-Hydroxy-3-methoxybenzyl)-4-[3-(trifluoromethyl)-pyridin-2-yl]piperazine-1-carboxamide

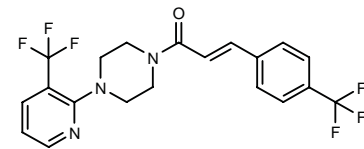


C19 H21 F3 N4 O3; Mol wt: 410.3939

ACTION – An antagonist of type 1 vanilloid receptors (VR1, also known as capsaicin receptors), expected to be useful as an analgesic agent, particularly in the treatment of neuropathic pain associated with postmastectomy pain syndrome, stump pain, phantom limb pain, oral neuropathic pain, Charcot's pain, toothache, postherpetic neuralgia, diabetic neuropathy, reflex sympathetic dystrophy, arthritis, fibromyalgia, Guillain-Barré syndrome, etc. Other exemplified compounds are:



Compound	R1	R2	R3	Formula
316549	H	CF3	H	C ₂₀ H ₂₃ F ₃ N ₄ O
316550	H	Cl	H	C ₁₉ H ₂₃ ClN ₄ O
316551	Cl	Cl	H	C ₁₉ H ₂₂ Cl ₂ N ₄ O
316552	H	Cl	Me	C ₂₀ H ₂₅ ClN ₄ O



316547: C20 H17 F6 N3 O

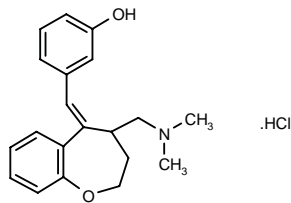
SOURCE – Neurogen.

REFERENCES

1. Hutchison, A. et al. (Neurogen Corp.) *Capsaicin receptor ligands*. WO 0208221.

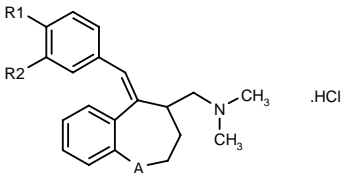
316650

(E)-3-[4-(Dimethylaminomethyl)-2,3,4,5-tetrahydro-1-benzoxepin-5-ylidenemethyl]phenol hydrochloride

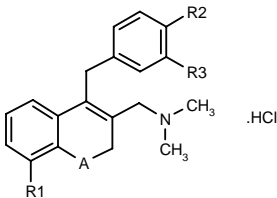


C20 H23 N O2 . HCl; Mol wt: 345.8676

ACTION – Analgesic agent that was able to suppress phenylquinone-induced writhing by 91% following i.v. administration to mice at 2.15 mg/kg. It is also described as useful for the treatment of urinary incontinence, pruritus, tinnitus and diarrhea. Other exemplified compounds are:



Compound	R1	R2	A	Isomer	Formula
316653	Cl	H	CH2	E	C ₂₁ H ₂₄ ClN.HCl
316655	Cl	H	O	Z	C ₂₀ H ₂₂ ClNO.HCl
316657	H	OH	O	Z	C ₂₀ H ₂₃ NO ₂ .HCl



Compound	R1	R2	R3	A	Formula
316651	H	Cl	H	-CH2-	C ₂₀ H ₂₂ ClN.HCl
316652	H	H	OH	-CH2-	C ₂₀ H ₂₃ NO.HCl
316654	OH	Cl	H	-CH2-	C ₂₀ H ₂₂ ClNO.HCl
316656	H	H	OH	-OCH2-	C ₂₀ H ₂₃ NO ₂ .HCl

SOURCE – Grünenthal.

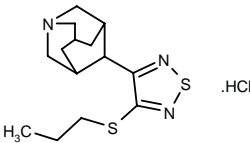
REFERENCES

1. Zimmer, O.K. et al. (Grünenthal GmbH) *Cyclic substd. aminomethyl cpds. and medicaments containing said cpds.*. DE 10033459, WO 0208218.

UCB-62106

294164

4-[4-(Propylsulfanyl)-1,2,5-thiadiazol-3-yl]-1-aza-tricyclo[3.3.1.1^{3,7}]decane hydrochloride



C14 H21 N3 S2 . HCl; Mol wt: 331.9338

ACTION – Analgesic agent, a selective muscarinic M₄ receptor agonist with marked antinociceptive activity in the rat tail-flick test (ED₅₀ = 0.018 mg/kg s.c.), but no significant muscarinic-like side effects. The antinociceptive activity was blocked by atropine methylnitrate given intracerebroventricularly or intrathecally, but not by s.c. administration, indicating that compound acts centrally at both spinal and supraspinal sites.

SOURCE – UCB.

REFERENCES

1. Grewal, G. et al. *Selective M4-agonists for treatment of pain*. 16th Int Symp Med Chem (Sept 18-22, Bologna) 2000, Abst PB-74.

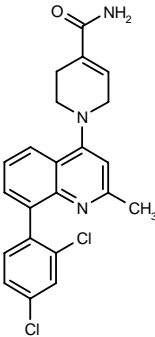
2. Zuo, F. et al. *Antinociceptive effect of UCB 62106, a novel muscarinic agonist analgesic, in mouse tail-flick assay*. 21st Annu Sci Meet Am Pain Soc (March 14-17, Baltimore) 2002, Abst 740.

PSYCHOPHARMACOLOGIC DRUGS

ANXIOLYTICS

315529

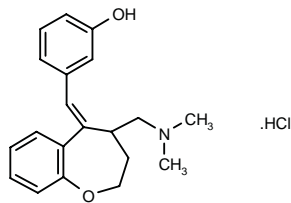
1-[8-(2,4-Dichlorophenyl)-2-methylquinolin-4-yl]-1,2,3,6-tetrahydropyridine-4-carboxamide



C22 H19 Cl2 N3 O; Mol wt: 412.3181

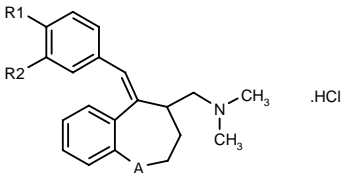
316650

(E)-3-[4-(Dimethylaminomethyl)-2,3,4,5-tetrahydro-1-benzoxepin-5-ylidenemethyl]phenol hydrochloride

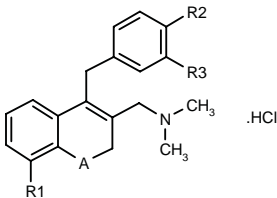


C20 H23 N O2 . HCl; Mol wt: 345.8676

ACTION – Analgesic agent that was able to suppress phenylquinone-induced writhing by 91% following i.v. administration to mice at 2.15 mg/kg. It is also described as useful for the treatment of urinary incontinence, pruritus, tinnitus and diarrhea. Other exemplified compounds are:



Compound	R1	R2	A	Isomer	Formula
316653	Cl	H	CH2	E	C ₂₁ H ₂₄ ClN.HCl
316655	Cl	H	O	Z	C ₂₀ H ₂₂ ClNO.HCl
316657	H	OH	O	Z	C ₂₀ H ₂₃ NO ₂ .HCl



Compound	R1	R2	R3	A	Formula
316651	H	Cl	H	-CH2-	C ₂₀ H ₂₂ ClN.HCl
316652	H	H	OH	-CH2-	C ₂₀ H ₂₃ NO.HCl
316654	OH	Cl	H	-CH2-	C ₂₀ H ₂₂ ClNO.HCl
316656	H	H	OH	-OCH2-	C ₂₀ H ₂₃ NO ₂ .HCl

SOURCE – Grünenthal.

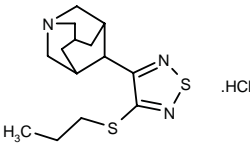
REFERENCES

1. Zimmer, O.K. et al. (Grünenthal GmbH) *Cyclic substd. aminomethyl cpds. and medicaments containing said cpds.*. DE 10033459, WO 0208218.

UCB-62106

294164

4-[4-(Propylsulfanyl)-1,2,5-thiadiazol-3-yl]-1-aza-tricyclo[3.3.1.1^{3,7}]decane hydrochloride



C14 H21 N3 S2 . HCl; Mol wt: 331.9338

ACTION – Analgesic agent, a selective muscarinic M₄ receptor agonist with marked antinociceptive activity in the rat tail-flick test (ED₅₀ = 0.018 mg/kg s.c.), but no significant muscarinic-like side effects. The antinociceptive activity was blocked by atropine methylnitrate given intracerebroventricularly or intrathecally, but not by s.c. administration, indicating that compound acts centrally at both spinal and supraspinal sites.

SOURCE – UCB.

REFERENCES

1. Grewal, G. et al. *Selective M4-agonists for treatment of pain*. 16th Int Symp Med Chem (Sept 18-22, Bologna) 2000, Abst PB-74.

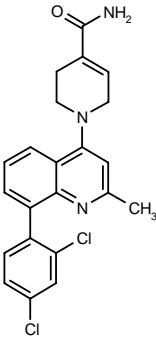
2. Zuo, F. et al. *Antinociceptive effect of UCB 62106, a novel muscarinic agonist analgesic, in mouse tail-flick assay*. 21st Annu Sci Meet Am Pain Soc (March 14-17, Baltimore) 2002, Abst 740.

PSYCHOPHARMACOLOGIC DRUGS

ANXIOLYTICS

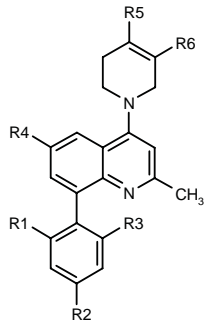
315529

1-[8-(2,4-Dichlorophenyl)-2-methylquinolin-4-yl]-1,2,3,6-tetrahydropyridine-4-carboxamide

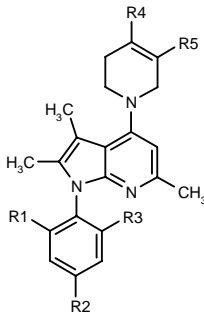


C22 H19 Cl2 N3 O; Mol wt: 412.3181

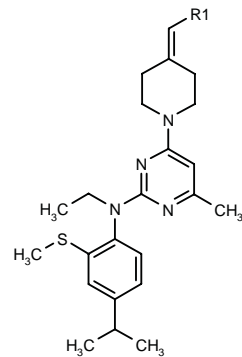
ACTION – Corticotropin-releasing factor (CRF) antagonist shown to display IC₅₀ values below 500 nM at CRF receptors in rat frontal cortex preparations. Potentially useful for the treatment of a variety of CRF-mediated conditions such as anxiety, depression, Alzheimer’s disease, Parkinson’s disease, Huntington’s chorea, eating disorders, hypertension, drug abuse, epilepsy, cerebral infarction, cerebral ischemia, cerebral edema, inflammation, immune diseases and alopecia, among others. Other exemplified tetrahydropyridino- and piperidino-containing compounds are:



Compound	R1	R2	R3	R4	R5	R6	Formula
315530	Me	Me	Me	H	CONH2	H	C ₂₅ H ₂₇ N ₃ O
315531	Cl	Cl	H	H	CH2CONH2	H	C ₂₃ H ₂₁ Cl ₂ N ₃ O
315532	Cl	CF3	H	H	CONH2	H	C ₂₃ H ₁₉ ClF ₃ N ₃ O
315533	Cl	OCF3	H	H	CONH2	H	C ₂₃ H ₁₉ ClF ₃ N ₃ O ₂
315534	Cl	Cl	H	Cl	CONH2	H	C ₂₂ H ₁₈ Cl ₃ N ₃ O
315535	Cl	Cl	H	Me	CONH2	H	C ₂₃ H ₂₁ Cl ₂ N ₃ O
315536	Cl	Cl	H	F	CONH2	H	C ₂₂ H ₁₈ Cl ₂ FN ₃ O
315537	Cl	Cl	H	H	H	CONH2	C ₂₂ H ₁₉ Cl ₂ N ₃ O
315538	Me	CF3	Me	H	H	CONH2	C ₂₅ H ₂₄ F ₃ N ₃ O



Compound	R1	R2	R3	R4	R5	Formula
315539	H	Cl	Cl	CONH2	H	C ₂₂ H ₂₂ Cl ₂ N ₄ O
315540	Cl	Cl	Cl	CONH2	H	C ₂₂ H ₂₁ Cl ₃ N ₄ O
315541	Cl	Br	Cl	CONH2	H	C ₂₂ H ₂₁ BrCl ₂ N ₄ O
315542	Br	Br	SMe	CONH2	H	C ₂₃ H ₂₄ Br ₂ N ₄ OS
315543	OMe	Br	Br	CONH2	H	C ₂₃ H ₂₄ Br ₂ N ₄ O ₂
315544	Br	Br	Br	CONH2	H	C ₂₂ H ₂₁ Br ₃ N ₄ O
315545	H	CF3	Br	CONH2	H	C ₂₃ H ₂₂ BrF ₃ N ₄ O
315546	Br	CF3	Br	CONH2	H	C ₂₃ H ₂₁ Br ₂ F ₃ N ₄ O
315547	H	Cl	Cl	H	CONH2	C ₂₂ H ₂₂ Cl ₂ N ₄ O



Compound	R1	Formula
315548	CO2Me	C ₂₅ H ₃₄ N ₄ O ₂ S
315549	CO2Et	C ₂₆ H ₃₆ N ₄ O ₂ S
315550	CN	C ₂₄ H ₃₁ N ₅ S

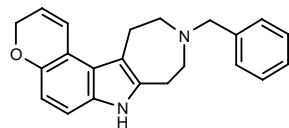
SOURCE – Taisho.

REFERENCES

1. Nakazato, A. et al. (Taisho Pharmaceutical Co., Ltd.) *Tetrahydropyridino or piperidino heterocyclic derivs.* WO 0202549.

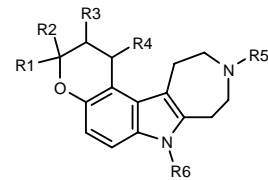
315872

10-Benzyl-7,8,9,10,11,12-hexahydro-3H-azepino-[4,5-b]pyrano[3,2-e]indole



C22 H22 N2 O; Mol wt: 330.4288

ACTION – Agent with affinity for 5-HT receptors and potential in the treatment of a variety of CNS disorders, particularly anxiety, obesity, depression and stress-related diseases. Other specifically claimed azepino[4,5-b]-pyrano[3,2-e]indole derivatives are:



Compound	R1=R2	R3	R4	R5	R6	Formula
315874	H	H	H	H	H	C ₁₅ H ₁₈ N ₂ O
315876	H	bond	CH2Ph	(CH2)4OPh		C ₃₂ H ₃₄ N ₂ O ₂
315878	H	bond	CH2Ph	CH2CO2Et		C ₂₆ H ₂₈ N ₂ O ₃
315880	H	bond	CH2Ph	CH2CO2H		C ₂₄ H ₂₄ N ₂ O ₃
315882	H	H	H	H	CH2CONHPh	C ₂₃ H ₂₅ N ₃ O ₂
315885	Me	bond		H	H	C ₁₇ H ₂₀ N ₂ O
315886	H	H	H	H	Ph	C ₂₁ H ₂₂ N ₂ O
315887	H	H	H	H	CH2Ph	C ₂₂ H ₂₄ N ₂ O

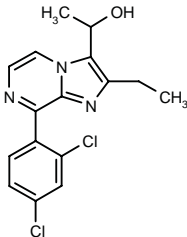
SOURCE – Pharmacia.

REFERENCES

1. Fu, J.-M. (Pharmacia Corp.) *Azepino[4,5-*b*]pyrano[3,2-*e*]indoles*. WO 0204456, WO 0204457.

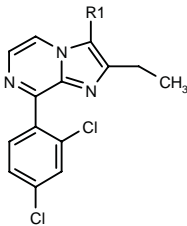
316075

1-[8-(2,4-Dichlorophenyl)-2-ethylimidazo[1,2-*a*]pyrazin-3-yl]ethanol



C16 H15 Cl2 N3 O; Mol wt: 336.2205

ACTION – Corticotropin-releasing factor (CRF) antagonist, potentially useful for the treatment of anxiety and depression. Other exemplified imidazo[1,2-*a*]pyrazine derivatives include the following:



Compound	R1	Formula
316076	CH(Me)OMe	C ₁₇ H ₁₇ Cl ₂ N ₃ O
316077	COPr	C ₁₈ H ₁₇ Cl ₂ N ₃ O
316078	C(=CH2)Pr	C ₁₉ H ₁₉ Cl ₂ N ₃
316079	N(Pr)CH2Ph	C ₂₄ H ₂₄ Cl ₂ N ₄

SOURCE – Bristol-Myers Squibb.

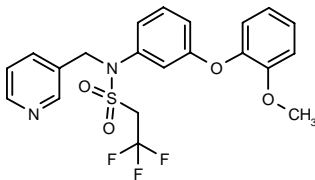
REFERENCES

1. Bakthavatchalam, R. et al. (DuPont Pharmaceuticals Co.) *Imidazo[1,2-*a*]pyrazines for the treatment of neurological disorders*. WO 0206286.

LY-508869*

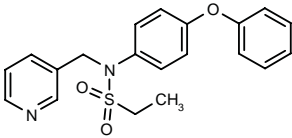
308167

2,2,2-Trifluoro-*N*-[3-(2-methoxyphenoxy)phenyl]-*N*-(pyridin-3-ylmethyl)ethanesulfonamide



C21 H19 F3 N2 O4 S; Mol wt: 452.4511

ACTION – Subtype-selective metabotropic glutamate mglu₂ receptor allosteric potentiator with an EC₅₀ value of 140 nM for binding to an allosteric site on the mglu₂ glutamate receptor. Potentially useful for the treatment of CNS disorders including anxiety, psychosis neurodegeneration, pain and epilepsy. Another related compound is:



LY-181837 [317991]: C20 H20 N2 O3 S

SOURCE – Lilly.

REFERENCES

1. Coleman, D.S. et al. (Eli Lilly and Company) *Potentiators of glutamate receptors*. WO 0156990.

2. Britton, T.C. et al. *Selective, non-amino-acid allosteric potentiators of mGlu2 receptors*. 223rd ACS Natl Meet (April 7-11, Orlando) 2002, Abst MEDI 153.

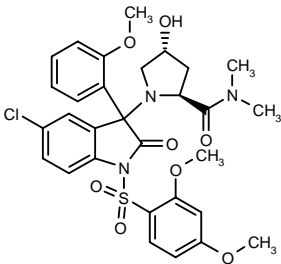
*Identified compound 308167 (see 308166) Drug Data Rep 2001, 023(10): 0953.

SSR-149415

309913

(-)-1-[5-Chloro-1-(2,4-dimethoxyphenylsulfonyl)-3-(2-methoxyphenyl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl]-4(*R*)-hydroxy-L-proline *N,N*-dimethylamide

SR-149415



C30 H32 Cl N3 O8 S; Mol wt: 630.1148

ACTION – Orally active, selective vasopressin V_{1b} receptor antagonist with high affinity for human (K_i = 1.5 and 4.2 nM in CHO cells and hypophysis, respectively) and animal V_{1b} receptors, and much lower affinity for V_{1a} (K_i = 91 nM in CHO cells expressing human receptor), V₂ (K_i = 1412 nM in CHO cells expressing human receptor) and oxytocin receptors (K_i = 174 nM in Ltk⁻ cells expressing human receptor); no affinity for a range of other receptors, enzymes and ion channels was found. Full competitive antagonist activity was seen in CHO cells, where it inhibited the arginine vasopressin (AVP)-induced increase in intracellular Ca²⁺ levels (K_i = 2.0 and 1.26 nM in cells expressing rat or human V_{1b} receptors, respectively). *In vivo*, compound was active in several models of elevated corticotropin secretion in rats; it inhibited the AVP-induced increase in plasma corticotropin levels at doses of 10 mg/kg p.o. or 3 mg/kg i.p., antagonized AVP-potentiated corticotropin release induced by corticoliberin at a dose of 3 mg/kg p.o. and

blocked corticotropin secretion induced by endogenous AVP levels subsequent to a rapid body water loss at 10 mg/kg p.o. It was also active in models of stress and anxiety in rats; a dose of 10 mg/kg i.p. significantly inhibited the restraint stress-induced elevation in corticotropin secretion in rats, and in the four-plate test in rats, a significant anxiolytic effect was seen at the dose of 3 mg/kg p.o. after acute or repeated administration. Potentially useful for the treatment of stress and anxiety.

SOURCE – Sanofi-Synthélabo.

REFERENCES

1. Roux, R. et al. (Sanofi-Synthélabo) *Novel 1,3-dihydro-2H-indol-2-one derivs., preparation method and pharmaceutical compsns. containing them.* FR 2804114, WO 0155130.

2. Griebel, G. et al. *Anxiolytic- and anti-depressant-like effects of the non-peptide vasopressin V_{1b} receptor antagonist, SSR149415, suggest an innovative approach for the treatment to stress-related disorders.* Proc Natl Acad Sci USA 2002, 99(9): 6370.

3. Serradeil-Le Gal, C. et al. *Characterization of (2S,4R)-1-[5-chloro-1-[(2,4-dimethoxyphenyl)sulfonyl]-3-(2-methoxy-phenyl)-2-oxo-2,3-dihydro-1H-indol-3-yl]-4-hydroxy-N,N-dimethyl-2-pyrrolidine carboxamide (SSR149415), a selective and orally active vasopressin V_{1b} receptor antagonist.* J Pharmacol Exp Ther 2002, 300(3): 1122.

4. *Information Meeting.* Sanofi-Synthelabo Web Site 2001, Sept 3.

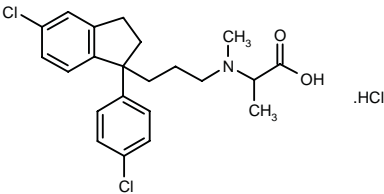
5. *R&D portfolio.* Sanofi-Synthelabo Web Site 2001, Aug 31.

6. *R&D portfolio.* Sanofi-Synthelabo Web Site 2002, March 1.

ANTIPSYCHOTIC DRUGS

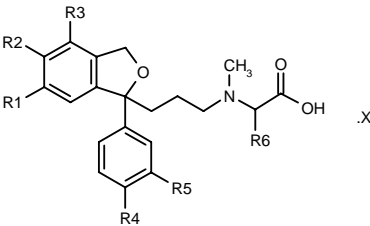
316442

N-[3-[5-Chloro-1-(4-chlorophenyl)indan-1-yl]propyl]-*N*-methyl-DL-alanine hydrochloride

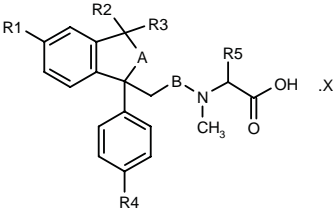


C22 H25 Cl2 N O2 . HCl; Mol wt: 442.8114

ACTION – A glycine transporter (GlyT) inhibitor shown to inhibit [³H]-glycine uptake by the GlyT-1b transporter with an IC₅₀ of 470 nM. Potentially useful for the treatment of schizophrenia, psychoses, dementia, pain, cognition disorders including Alzheimer’s disease, multiinfarct dementia, AIDS dementia, Huntington’s disease, Parkinson’s disease, amyotrophic lateral sclerosis, head trauma and stroke. Other exemplified compounds are:



Compound	R1	R2	R3	R4	R5	R6	X	Formula
316443	H	H	H	Me	H	H	HCl	C ₂₁ H ₂₈ NO ₃ .HCl
316444	H	H	Cl	Cl	H	H	HCl	C ₂₀ H ₂₁ Cl ₂ NO ₃ .HCl
316445	H	Cl	H	Cl	H	Me	HCl	C ₂₁ H ₂₃ Cl ₂ NO ₃ .HCl
316446	Cl	H	H	Cl	H	H	HCl	C ₂₀ H ₂₁ Cl ₂ NO ₃ .HCl
316447	Cl	H	H	Me	H	H	HCl	C ₂₁ H ₂₄ ClNO ₃ .HCl
316448	H	CN	H	F	Me	H	HCl	C ₂₂ H ₂₃ FN ₂ O ₃ .HCl
316449	H	CN	H	OMe	H	H	HCl	C ₂₂ H ₂₄ N ₂ O ₄ .HCl
316451	H	Br	H	Cl	H	H		C ₂₀ H ₂₁ BrClNO ₃
316456	H	4-Me-Ph	H	Cl	H	H		C ₂₇ H ₂₈ ClNO ₃



Compound	R1	R2	R3	R4	R5	A	B	X	Formula
316450	Cl	H	H	Cl	H	CH2	-(CH2)2-	HCl	C ₂₁ H ₂₃ Cl ₂ NO ₂ .HCl
316452	H	Me	Me	Cl	H	O	-CH2-		C ₂₁ H ₂₄ ClNO ₃
316453	H	Me	H	H	Me	CH2	-CH2-		C ₂₂ H ₂₇ NO ₂
316454	4-Me-Ph	H	H	Cl	H	O	-CH2-		C ₂₆ H ₂₆ ClNO ₃
316455	2-thienyl	H	H	Cl	H	O	-CH2-		C ₂₃ H ₂₂ ClNO ₃ S
316457	2-Me-Ph	H	H	Cl	H	O	-CH2-		C ₂₆ H ₂₆ ClNO ₃
316458	2,5-(Cl)2-Ph	H	H	Cl	H	O	-CH2-		C ₂₆ H ₂₂ Cl ₃ NO ₃

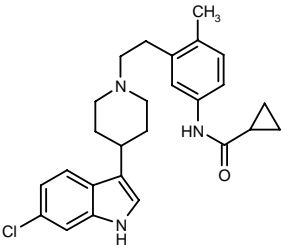
SOURCE – Lundbeck.

REFERENCES

1. Moltzen, E.K. et al. (H. Lundbeck A/S) *Novel cpds. and their use as glycine transport inhibitors.* WO 0208216.

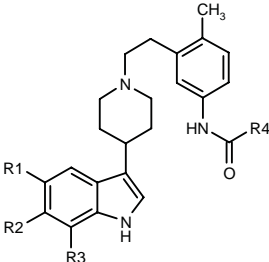
316687

N-[3-[2-[4-(6-Chloro-1*H*-indol-3-yl)piperidin-1-yl]ethyl]-4-methylphenyl]cyclopropanecarboxamide



C26 H30 Cl N3 O; Mol wt: 435.9960

ACTION – Dopamine D4 receptor antagonist shown to inhibit the binding of [³H]-YM-09151-2 to D4 receptors in CHO cells by 99% at 50 nM. Potentially useful for the treatment of schizophrenia and other psychoses, anxiety, panic disorders, obsessive–compulsive disorder, depression, aggression, side effects induced by conventional antipsychotic agents, migraine, cognitive disorders, attention deficit hyperactivity disorder and sleep disorders. Other exemplified indole derivatives are:



Compound	R1	R2	R3	R4	Formula
316690	F	H	H	i-Pr	C ₂₆ H ₃₂ FN ₃ O
316691	F	H	H	3-MeO-Ph	C ₃₀ H ₃₂ FN ₃ O ₂
316692	F	H	H	3-Pyr	C ₂₈ H ₂₉ FN ₄ O
316693	H	Cl	H	2-thienyl	C ₂₇ H ₂₈ ClN ₃ OS
316694	H	Cl	H	i-Pr	C ₂₆ H ₃₂ ClN ₃ O
316695	H	Cl	H	3-Pyr	C ₂₈ H ₂₉ ClN ₄ O
316696	H	Cl	H	cyclopentyl	C ₂₈ H ₃₄ ClN ₃ O
316697	F	H	H	4-morpholinyl	C ₂₇ H ₃₃ FN ₄ O ₂
316698	H	H	Cl	C ₅ H ₁₁	C ₂₈ H ₃₆ ClN ₃ O
316699	F	H	H	4-THP	C ₂₈ H ₃₄ FN ₃ O ₂
316700	F	H	H	cyclohexyl-CH ₂ CH ₂	C ₃₁ H ₄₀ FN ₃ O
316701	H	H	Cl	4-Me-Ph	C ₃₀ H ₃₂ ClN ₃ O
316702	H	H	Cl	cyclopropyl	C ₂₆ H ₃₀ ClN ₃ O

SOURCE – Lundbeck.

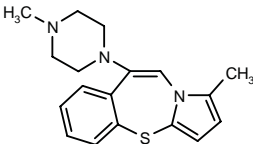
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ST-2092

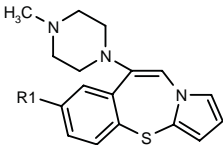
316806

1-Methyl-9-(4-methylpiperazin-1-yl)pyrrolo[2,1-*b*][1,3]-benzothiazepine



C18 H21 N3 S; Mol wt: 311.4509

ACTION – Atypical antipsychotic agent reported to display higher affinity for 5-HT_{2A} receptors than for dopamine receptors involved in extrapyramidal side effects of antipsychotic agents. It displayed a K_i of 1.1 nM against 5-HT_{2A} receptors, and exhibited 140-, 110- and 16-fold selectivity, respectively, over dopamine D1, D2 and D3 receptors. Other exemplified pyrrolo[2,1-*b*][1,3] derivatives are:



Compound	R1	Formula
ST-1899 [316808]	H	C ₁₇ H ₁₉ N ₃ S
ST-1928 [316810]	F	C ₁₇ H ₁₈ FN ₃ S

SOURCE – Sigma-Tau.

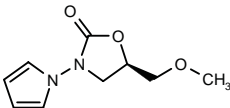
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TREATMENT OF MOOD DISORDERS

316728

5(*R*)-((Methoxymethyl)-3-(1*H*-pyrrol-1-yl)oxazolidin-2-one



C9 H12 N2 O3; Mol wt: 196.2048

ACTION – Potent, selective and irreversible inhibitor of monoamine oxidase (MAO) type A (K_i = 4.9 and 50,000 nM against MAO-A and MAO-B, respectively) with comparable potency to befloxatone but much higher selectivity for the MAO-A isozyme (K_i = 2.5 and 220 nM, respectively). Potentially useful as an antidepressant.

SOURCES – Università degli Studi “La Sapienza”, Rome (IT); Università degli Studi di Salerno, Salerno (IT); Università degli Studi di Siena, Siena (IT).

REFERENCES

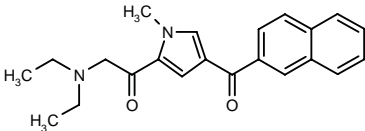
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NEUROLOGIC DRUGS

ANTIEPILEPTIC DRUGS

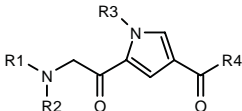
315803

2-(Diethylamino)-1-[1-methyl-4-(naphthalen-2-ylcarbon-yl)-1*H*-pyrrol-2-yl]ethanone

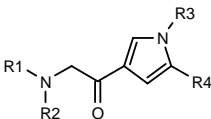


C22 H24 N2 O2; Mol wt: 348.4436

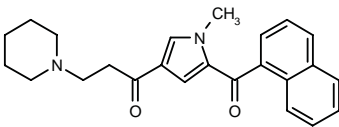
ACTION – Agent for the treatment of CNS disorders, particularly epilepsy and neuropathic pain. Compound demonstrated *in vivo* activity in the mouse maximal electroshock seizure test (ED₅₀ = 10.98 mg/kg i.p.) and in a rat model of neuropathic pain. Other specifically claimed acyl-substituted pyrrole derivatives are:



Compound	R1	R2	R3	R4	Formula
315806	Et	Et	Me	2-thienyl	C ₁₆ H ₂₀ N ₂ O ₂ S
315807	Et	Et	Me	1-Naph	C ₂₂ H ₂₄ N ₂ O ₂
315808	-(CH2)5-		Me	1-Naph	C ₂₃ H ₂₄ N ₂ O ₂
315809	-(CH2)5-		CH2CH2N(Me)2	2-Naph	C ₂₆ H ₃₁ N ₃ O ₂
315828	-(CH2)5-		Me	2-Naph	C ₂₃ H ₂₄ N ₂ O ₂
315830	-(CH2)5-		Me	5-Cl-2-thienyl	C ₁₇ H ₁₉ ClN ₂ O ₂ S



Compound	R1	R2	R3	R4	Formula
315810	Et	Et	Me	5-Cl-2-thienyl	C ₁₅ H ₁₉ ClN ₂ OS
315811	-CH2CH2-N(Me)CH2CH2-		Me	4-Cl-PhCO	C ₁₉ H ₂₂ ClN ₃ O ₂
315815	Et	Et	CH2CH2OMe	4-Cl-PhCO	C ₂₀ H ₂₅ ClN ₂ O ₃
315816	Et	Et	Me	2-thienyl-CO	C ₁₆ H ₂₀ N ₂ O ₂ S
315817	-(CH2)5-		Me	2-thienyl-CO	C ₁₇ H ₂₀ N ₂ O ₂ S
315819	Et	Et	Me	3-Pyr-CO	C ₁₇ H ₂₁ N ₃ O ₂
315820	Et	Et	Me	2-Naph-CO	C ₂₂ H ₂₄ N ₂ O ₂
315822	-(CH2)5-		(CH2)3N(Me)2	4-Cl-PhCO	C ₂₃ H ₃₀ ClN ₃ O ₂
315823	Me	Et	Me	2-Naph-CO	C ₂₁ H ₂₂ N ₂ O ₂
315826	Et	Et	CH2CH2SMe	2-Cl-PhCO	C ₂₀ H ₂₅ ClN ₂ O ₂ S



315812: C24 H26 N2 O2

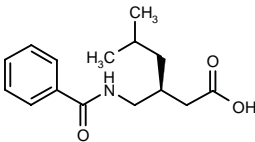
SOURCE – Ortho-McNeil.

REFERENCES

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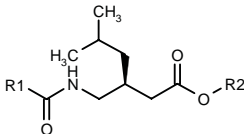
316386

3(*S*)-(Benzamidomethyl)-5-methylhexanoic acid



C15 H21 N O3; Mol wt: 263.3349

ACTION – GABA-related prodrug, potentially useful for the treatment of epilepsy, faintness attacks, hypokinesia, cranial disorders, neurodegenerative disorders, depression, anxiety, panic, pain, neuropathological disorders and digestive disorders. Other specifically claimed alkyl amino acids are:



Compound	R1	R2	Formula
316388	Ph	CH2Ph	C ₂₂ H ₂₇ NO ₃
316389	OCH2OAc	H	C ₁₂ H ₂₁ NO ₆
316390	t-BuCOOCH2O	H	C ₁₅ H ₂₇ NO ₆
316392	OCH2OCOPh	H	C ₁₇ H ₂₃ NO ₆

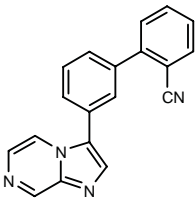
SOURCE – Pfizer.

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1. Bryans, J.S. et al. (Pfizer Inc.) *Alkyl amino acid derivs. useful as pharmaceutical agents.* EP 1178034.

316801

3'-(Imidazo[1,2-*a*]pyrazin-3-yl)biphenyl-2-carbonitrile



C19 H12 N4; Mol wt: 296.3318

ACTION – A representative compound within a group of 3-phenylimidazo[1,2-*a*]pyrazine derivatives with affinity for the $\alpha 2$ and/or $\alpha 3$ subunits of GABA_A receptors. Potentially useful for the treatment of anxiety and convulsions.

SOURCE – Merck Sharp & Dohme.

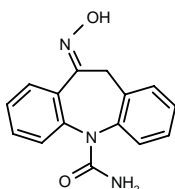
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BIA-2-024*

259902

10(*E*)-(Hydroxyimino)-10,11-dihydro-5*H*-dibenzo[*b,f*]azepine-5-carboxamide



C15 H13 N3 O2; Mol wt: 267.2867

ACTION – Antiepileptic agent structurally related to oxcarbazepine, with sodium channel-dependent inhibitory activity on the release of endogenous glutamate in rat hippocampal synaptosomes. Neurotoxicity studies in cultured hippocampal neurons showed that compound was less toxic than carbamazepine and oxcarbazepine. Pharmacokinetic studies in rats, mice and rabbits demonstrated rapid absorption after oral administration; it was much more stable in mice than in rats, where it was rapidly metabolized to the inactive nitro derivative followed by transformation to oxcarbazepine. Metabolic studies in human liver microsomes showed a very slow rate of metabolism. It is expected that in humans compound would be absorbed efficiently and excreted mainly as the parent compound, with relatively low hepatic clearance.

SOURCES – Bial; Portela.

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1. Benes, J. et al. (Portela & Ca., SA) *New derivs. of 10,11-dihydro-10-oxo-5H-dibenz[*b,f*]azepine-5-carboxamide*. EP 0810216, JP 1998081669, US 5866566, WO 9745416.
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5. Hainzl, D. et al. *Metabolism of 10,11-dihydro-10-hydroxyimino-5H-dibenz[*b,f*]azepine-5-carboxamide, a potent anti-epileptic drug*. Xenobiotica 2002, 32(2): 131.
6. Learmonth, D.A. et al. *Synthesis, anticonvulsant properties and pharmacokinetic profile of novel 10,11-dihydro-10-oxo-5H-dibenz[*b,f*]azepine-5-carboxamide derivatives*. Eur J Med Chem 2001, 36(3): 227.

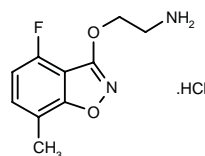
*Identified compound **259902** Drug Data Rep 1998, 020(03): 0206.

TREATMENT OF EXTRAPYRAMIDAL MOVEMENT DISORDERS

RS-1653

316973

2-(4-Fluoro-7-methyl-1,2-benzisoxazol-3-yloxy)ethanamine hydrochloride



C10 H11 F N2 O2 . HCl; Mol wt: 246.6678

ACTION – Dual inhibitor of monoamine oxidase A (MAO-A) and B (MAO-B) able to improve the parkinsonian syndrome in MPTP-treated marmosets. A dose of 30 mg/kg i.p. increased spontaneous locomotor activity on its own and enhanced the effect of low doses of L-DOPA (2.5 mg/kg i.p.). Potentially useful for the treatment of Parkinson's disease.

SOURCE – Sankyo.

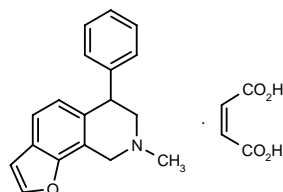
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2. Kojima, K. et al. (Sankyo Co., Ltd.) *Monoamineoxidase inhibitor*. JP 1997227534.
3. Ando, K. et al. *Inhibition of both MAO-A and -B in the brain improved parkinsonian syndrome in common marmosets*. Jpn J Pharmacol 2002, 88(Suppl. 1): Abst P-142.
4. Yoshimi, K. et al. *Novel monoamine oxidase inhibitors, 3-(2-aminoethoxy)-1,2-benzisoxazole derivatives, and their differential reversibility*. Jpn J Pharmacol 2002, 88(2): 174.

TREATMENT OF ATTENTION DEFICIT HYPERACTIVITY DISORDER

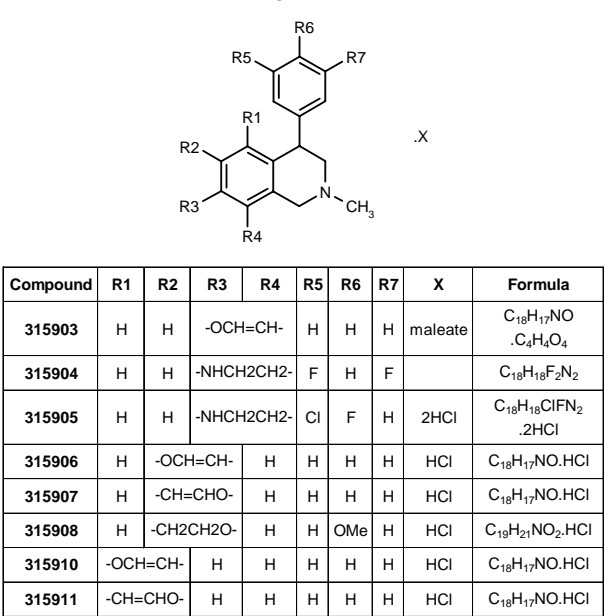
315902

8-Methyl-6-phenyl-6,7,8,9-tetrahydrofuro[3,2-*h*]isoquinoline maleate



C18 H17 N O . C4 H4 O4; Mol wt: 379.4099

ACTION – Modulator of the reuptake of noradrenaline, dopamine and 5-HT, potentially useful for the treatment of attention deficit hyperactivity disorder (ADHD). Other applications include anxiety, depression, posttraumatic stress disorder, supranuclear palsy, eating disorders, obsessive–compulsive disorder, pain, smoking cessation, panic attacks, Parkinson’s disease and phobia. Other exemplified 4-phenyl-1,2,3,4-tetrahydroisoquinoline derivatives include the following:



SOURCE – Bristol-Myers Squibb.

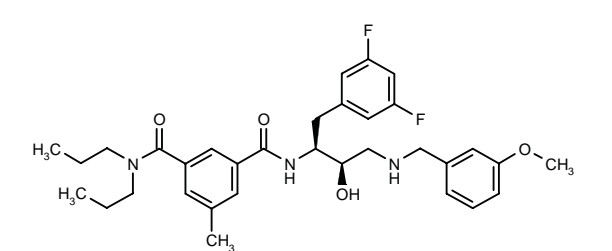
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TREATMENT OF
COGNITION DISORDERS

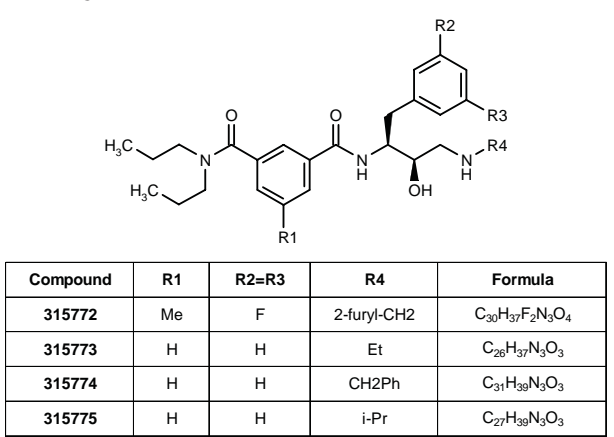
315767

*N*¹-[1(*S*)-(3,5-Difluorobenzyl)-2(*R*)-hydroxy-3-(3-methoxybenzylamino)propyl]-5-methyl-*N*³,*N*³-dipropylisophthalamide



C33 H41 F2 N3 O4; Mol wt: 581.6999

ACTION – An inhibitor of the formation of β-amyloid (Aβ) deposits, potentially useful for the treatment of Alzheimer’s disease, mild cognitive impairment, Down’s syndrome, hereditary cerebral hemorrhage with amyloidosis of the Dutch type, cerebral amyloid angiopathy and other degenerative dementias. Other exemplified hydroxyamino compounds include the following:



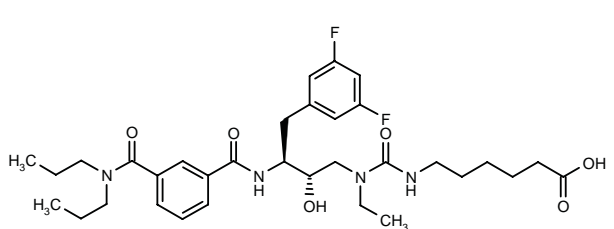
SOURCES – Elan; Pharmacia.

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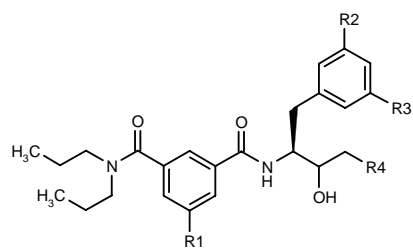
315813

6-[3-[4-(3,5-Difluorophenyl)-3(*S*)-[3-(*N,N*-dipropyl-carbamoyl)benzamido]-2(*S*)-hydroxybutyl]-3-ethylureido]-hexanoic acid



C33 H46 F2 N4 O6; Mol wt: 632.7444

ACTION – Agent with the ability to inhibit the formation of β-amyloid (Aβ) deposits, potentially useful for the treatment of Alzheimer’s disease, as well as other Aβ-mediated disorders including Down’s syndrome, hereditary cerebral hemorrhage with amyloidosis of the Dutch type, cerebral amyloid angiopathy and other degenerative dementias. Other exemplified compounds include the following:



Compound	R1	R2=R3	R4	Isomer	Formula
315814	H	F	i-BuNHCON(Et)	S	C ₃₁ H ₄₄ F ₂ N ₄ O ₄
315818	Me	F	N(Et)SO ₂ Bu	S	C ₃₁ H ₄₅ F ₂ N ₃ O ₅ S
315821	Me	F	2(S)-(i-BuNHCO)-1-Pip	R	C ₃₅ H ₅₀ F ₂ N ₄ O ₄
315824	Me	F	4-Me-1-Piz	R	C ₃₀ H ₄₂ F ₂ N ₄ O ₃
315825	Me	F	i-BuNHCOCH ₂ N(Me)	R	C ₃₂ H ₄₆ F ₂ N ₄ O ₄
315827	Me	F	(S)-i-BuNHCOCH(Me)N(Me)	R	C ₃₃ H ₄₈ F ₂ N ₄ O ₄
315829	H	H	3-thiazolidinyl	R	C ₂₇ H ₃₇ N ₃ O ₃ S
315831	H	H	4-(4-F-Ph)-1-Piz	R	C ₃₄ H ₄₃ FN ₄ O ₃

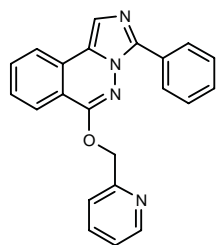
SOURCES – Elan; Pharmacia.

REFERENCES

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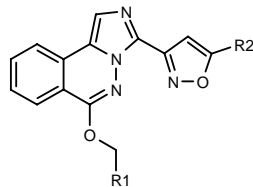
316069

3-Phenyl-6-(pyridin-2-ylmethoxy)imidazo[5,1-a]-phthalazine



C22 H16 N4 O; Mol wt: 352.3954

ACTION – Agent with high affinity for the α5 subunit of GABA_A receptors that acts as a partial or full inverse agonist at this subunit, while acting as an antagonist at α1, α2 and α3 subunits. Potentially useful for the treatment of cognition deficits associated with Alzheimer’s disease, and also with other conditions including traumatic injury, stroke, Parkinson’s disease, Down’s syndrome, age-related memory deficits and attention deficit hyperactivity disorder. Other exemplified imidazo[5,1-a]phthalazine derivatives are:



Compound	R1	R2	Formula
316070	3-MeO-2-Pyr	Me	C ₂₁ H ₁₇ N ₅ O ₃
316071	1-Me-1,2,4-triazol-3-yl	H	C ₁₇ H ₁₃ N ₇ O ₂

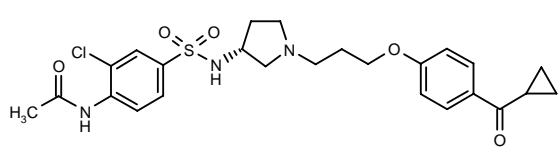
SOURCE – Merck Sharp & Dohme.

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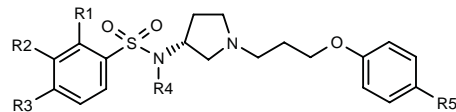
316143

N-[2-Chloro-4-[N-[1-[3-[4-(cyclopropylcarbonyl)phenoxy]-propyl]pyrrolidin-3(R)-yl]sulfamoyl]phenyl]acetamide



C25 H30 Cl N3 O5 S; Mol wt: 520.0470

ACTION – Agent with affinity for histamine H₃ receptors that displayed a K_i of 1.2 nM against H₃ receptors in rat cortical membranes. Potentially useful for the treatment of Alzheimer’s disease, attention deficit hyperactivity disorder, epilepsy and narcolepsy, as well as other H₃-mediated conditions including myocardial infarction, asthma, cutaneous carcinoma, depression, inflammation, medullary thyroid carcinoma, melanoma, Ménière’s disease, migraine, motion sickness, obesity, pain, Parkinson’s disease, schizophrenia, seizures and septic shock. Other exemplified pyrrolidines are:



Compound	R1	R2	R3	R4	R5	Formula
316144	H	H	H	H	cyclopropyl-CO	C ₂₃ H ₂₈ N ₂ O ₄ S
316145	H	H	i-Pr	H	cyclopropyl-CO	C ₂₆ H ₃₄ N ₂ O ₄ S
316146	F	H	H	H	cyclopropyl-CO	C ₂₃ H ₂₇ FN ₂ O ₄ S
316147	H	CN	H	H	cyclopropyl-CO	C ₂₄ H ₂₇ N ₃ O ₄ S
316148	H	OMe	OMe	H	cyclopropyl-CO	C ₂₅ H ₃₂ N ₂ O ₆ S
316149	H	Me	H	H	cyclopropyl-CO	C ₂₄ H ₃₀ N ₂ O ₄ S
316150	H	H	SO ₂ Me	Me	4-CN-Ph	C ₂₈ H ₃₁ N ₃ O ₅ S ₂

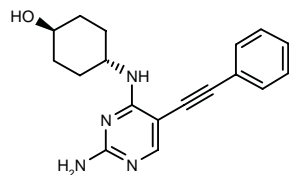
SOURCE – Abbott.

REFERENCES

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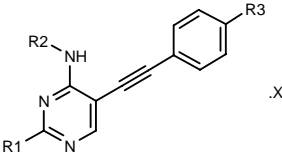
316460

trans-4-[2-Amino-5-(phenylethynyl)pyrimidin-4-ylamino]-cyclohexanol



C18 H20 N4 O; Mol wt: 308.3830

ACTION – Agent with nerve growth factor (NGF)-like activity that was shown to increase choline acetyltransferase (ChAT) activity by 100% in PC-12 cells over the activity with NGF alone at 0.1 μM. Potentially useful for the treatment of central and peripheral nervous system disorders such as Alzheimer’s disease, peripheral neuropathy, senile dementia and seizures, as well as diabetes. Other exemplified 5-alkynylpyrimidine derivatives are:



Compound	R1	R2	R3	X	Formula
316461	H	trans-4-OH-cyclohexyl	Cl		C ₁₈ H ₁₈ ClN ₃ O
316462	NH2	trans-4-OH-cyclohexyl	Cl		C ₁₈ H ₁₉ ClN ₄ O
316463	NH2	CH2CH2OH	Cl		C ₁₄ H ₁₃ ClN ₄ O
316465	NH2	CH2CH2OCH2CH2OH	Cl		C ₁₈ H ₁₇ ClN ₄ O ₂
316466	NH2	cis-4-OH-cyclohexyl	Cl		C ₁₈ H ₁₉ ClN ₄ O
316468	NH2	trans-4-OH-cyclohexyl	Et	HCl	C ₂₀ H ₂₄ N ₄ O.HCl

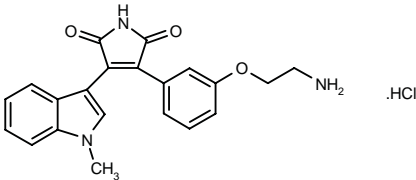
SOURCE – Krenitsky Pharmaceuticals.

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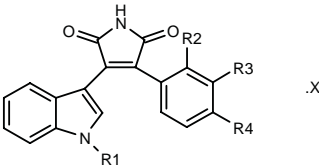
316869

3-[3-(2-Aminoethoxy)phenyl]-4-(1-methyl-1*H*-indol-3-yl)-2,5-dihydro-1*H*-pyrrole-2,5-dione hydrochloride



C21 H19 N3 O3 . HCl; Mol wt: 397.8600

ACTION – A glycogen synthase kinase-3β (GSK-3β) inhibitor (IC₅₀ = 0.02 μM), potentially useful for the treatment of asthma, allergy and allergic rhinitis, as well as other GSK-3β-mediated conditions including Alzheimer’s disease, obesity, diabetes, atherosclerosis, polycystic ovary syndrome, syndrome X, ischemia, brain trauma, bipolar disorder, immunodeficiency and cancer. Other exemplified compounds are:



Compound	R1	R2	R3	R4	X	Formula
316870	Me	OCH2CH-(OH)CH2OH	H	H		C ₂₂ H ₂₀ N ₂ O ₅
316871	Me	H	O(CH2)3NH2	H	HCl	C ₂₂ H ₂₁ N ₃ O ₃ .HCl
316872	Me	H	4-morpholinyl-CH2CH2O	H		C ₂₅ H ₂₅ N ₃ O ₄
316873	H	H	4-morpholinyl-CH2CH2O	H		C ₂₄ H ₂₃ N ₃ O ₄
316874	Me	H	H	(R)-2,2-(Me)2-1,3-dioxan-4-yl-CH2O		C ₂₆ H ₂₆ N ₂ O ₅

SOURCE – Roche.

REFERENCES

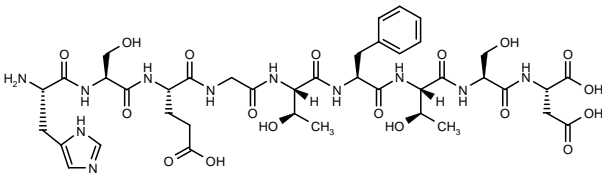
1. Gong, L. et al. (F. Hoffmann-La Roche AG) *3-Indolyl-4-phenyl-1H-pyrrole-2,5-dione derivs. as inhibitors of glycogen synthase kinase-3β.* WO 0210158.

GILATIDE

302421

L-Histidyl-L-seryl-L-glutamyl-glycyl-L-threonyl-L-phenylalanyl-L-threonyl-L-seryl-L-aspartic acid

GILA



C40 H57 N11 O18; Mol wt: 979.9493

ACTION – Nootropic agent, a truncated peptide consisting of 9 amino acid residues homologous with discrete domains of peptides (exendin-4, glucagon-like peptide), able to stimulate the CREB (cyclic adenosine monophosphate [cAMP] response element-binding protein) pathway involved in learning and memory. The peptide has been shown to markedly improve memory in healthy rodents. In the Morris water maze, intranasal peptide enhanced spatial memory, activated hippocampal transcription factors that mediated learning and memory, and induced genes implicated in neuronal plasticity.

SOURCES – Axonyx; Thomas Jefferson University, Philadelphia, PA (US).

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2. Haile, C.N. and During, M.J. *Gilatide: A novel peptide with memory enhancing properties.* Soc Neurosci Abst 2000, 26(Part 1): Abst 373.4.

3. Haile, C.N. et al. *Gilatide: A novel nootropic peptide.* Soc Neurosci Abst 2001, 27: Abst 78.15.

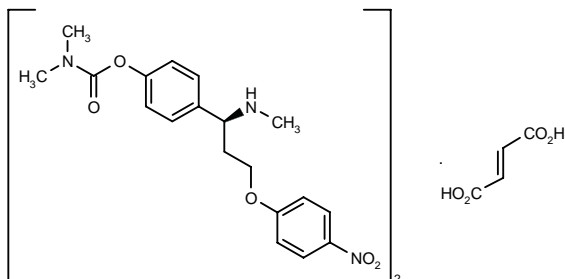
4. *Axonix updates phenserine development progress.* DailyDrugNews.com (Daily Essentials) 2001, Sept 6.

5. *Novel memory-enhancing technology licensed by Axonix from TJU.* DailyDrugNews.com (Daily Essentials) 2001, April 23.

RS-1259

316972

N,N-Dimethylcarbamic acid 4-[1(*S*)-(methylamino)-3-(4-nitrophenoxy)propyl]phenyl ester hemifumarate



2 C19 H23 N3 O5 . C4 H4 O4; Mol wt: 862.8850

ACTION – Orally active dual inhibitor of acetylcholinesterase (AChE) and 5-HT uptake with the ability to improve memory deficits in the place discrimination task in 24-month-old rats. Potentially useful for the treatment of Alzheimer's disease.

SOURCE – Sankyo.

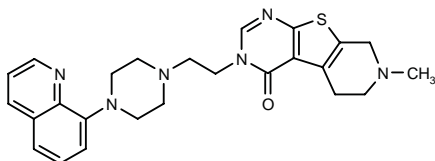
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TREATMENT OF Cerebrovascular Diseases

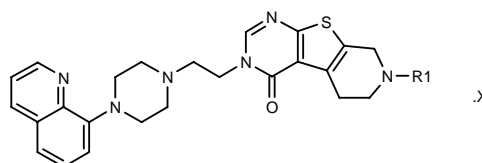
315353

7-Methyl-3-[2-[4-(8-quinoliny)piperazin-1-yl]ethyl]-3,4,5,6,7,8-hexahydropyrido[4',3':4,5]thieno[2,3-*d*]pyrimidin-4-one



C25 H28 N6 O S; Mol wt: 460.6032

ACTION – Agent with affinity for 5-HT_{1A} receptors (K_i = 0.15 nM), potentially useful for the treatment of cerebral ischemia, as well as neurodegenerative diseases and brain trauma. Other exemplified substituted thienopyrimidine derivatives are:



Compound	R1	X	Formula
315354	H		C ₂₄ H ₂₆ N ₆ OS
315355	Et	2HCl	C ₂₆ H ₃₀ N ₆ OS.2HCl

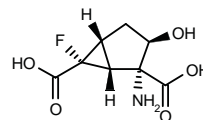
SOURCE – Abbott.

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1. Steiner, G. et al. (Knoll AG) *Substd. thienopyrimidine derivs. and the use thereof for the prophylaxis and therapy of cerebral ischaemia.* DE 10031389, WO 0202569.

315422

(1*R*,2*R*,3*R*,5*R*,6*R*)-2-Amino-6-fluoro-3-hydroxybicyclo-[3.1.0]hexane-2,6-dicarboxylic acid



C8 H10 F N O5; Mol wt: 219.1670

ACTION – A representative compound from a series of bicyclo[3.1.0]hexane-2,6-dicarboxylic acid derivatives that acts as an agonist at group II metabotropic glutamate receptors. It was shown to inhibit forskolin-stimulated accumulation of cAMP in CHO cells with an IC₅₀ of 476 nM. Potentially useful for the treatment of psychiatric and neurological disorders such as schizophrenia, anxiety, depression, bipolar disorder, drug abuse, Alzheimer's disease, Huntington's chorea, Parkinson's disease, muscular rigidity, cerebral ischemia, and head and spinal cord trauma.

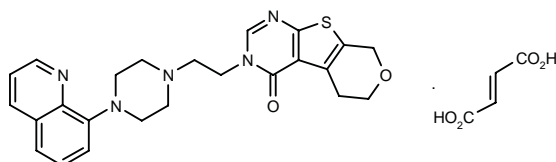
SOURCE – Taisho.

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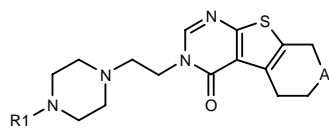
315726

3-[2-[4-(8-Quinoliny)piperazin-1-yl]ethyl]-4,5,6,8-tetrahydro-3*H*-pyrano[4',3':4,5]thieno[2,3-*d*]pyrimidin-4-one fumarate

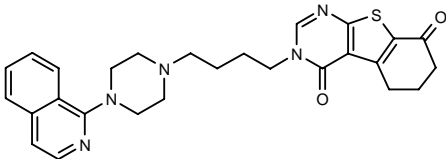


C24 H25 N5 O2 S . C4 H4 O4; Mol wt: 563.6321

ACTION – Agent with high affinity for 5-HT_{1A} receptors (K_i = 0.16 nM against receptors expressed in HEK293 cells), potentially useful for the treatment of neurodegenerative diseases, brain trauma and cerebral ischemia. Other exemplified pyrimidine derivatives include the following:



Compound	R1	A	Formula
315731	1-isoquinolyl	-O-	C ₂₄ H ₂₅ N ₅ O ₂ S
315732	1-isoquinolyl	-S(O)-	C ₂₄ H ₂₅ N ₅ O ₂ S ₂
315733	1-isoquinolyl	-N(SO ₂ Me)-	C ₂₅ H ₂₈ N ₆ O ₃ S ₂
315735	8-quinolyl	-S-	C ₂₄ H ₂₅ N ₅ OS ₂
315738	8-quinolyl	-S(O)-	C ₂₄ H ₂₅ N ₅ O ₂ S ₂
315740	8-quinolyl	-N(SO ₂ Me)-	C ₂₅ H ₂₈ N ₆ O ₃ S ₂



315730: C27 H29 N5 O2 S

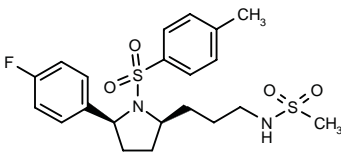
SOURCE – Abbott.

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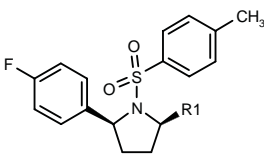
315763

N-[3-[(2*R**,5*R**)-5-(4-Fluorophenyl)-1-(4-methylphenyl)sulfonyl]pyrrolidin-2-yl]propyl]methanesulfonamide

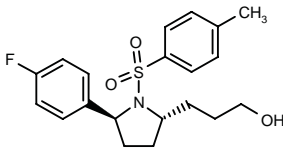


C21 H27 F N2 O4 S2; Mol wt: 454.5843

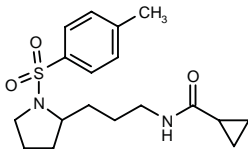
ACTION – A group I metabotropic glutamate receptor (mglu) agonist with an EC₅₀ of 0.16 μM at rat mglu_{1a} receptors expressed in EBNA cells. Potentially useful for the treatment of restricted brain function associated with bypass operations or poor blood supply, spinal cord and head trauma, hypoxia caused by pregnancy, cardiac arrest, hypoglycemia, Alzheimer’s disease, Huntington’s chorea, amyotrophic lateral sclerosis, AIDS dementia, eye injuries, retinopathy, cognitive disorders, memory deficits, pain, schizophrenia, parkinsonism and conditions which lead to glutamate deficiency functions such as muscle spasms, convulsions, migraine, urinary incontinence, nicotine and opiate addiction, psychosis, anxiety, vomiting, dyskinesia and depression. Other exemplified sulfonylpyrrolidine derivatives are:



Compound	R1	Isomer	Formula
315764	CN	2 <i>R</i> *,5 <i>S</i> *	C ₁₈ H ₁₇ FN ₂ O ₂ S
315766	CH ₂ Cl	2 <i>R</i> *,5 <i>S</i> *	C ₁₈ H ₁₉ ClFNO ₂ S
315769	cyclopropyl-CONHCH ₂	2 <i>R</i> *,5 <i>S</i> *	C ₂₂ H ₂₅ FN ₂ O ₃ S
315770	5-Me-1,2,4-oxadiazol-3-yl-CH ₂	2 <i>R</i> *,5 <i>S</i> *	C ₂₁ H ₂₂ FN ₃ O ₃ S
315776	2-Me-5-tetrazolyl-CH ₂	2 <i>R</i> *,5 <i>S</i> *	C ₂₀ H ₂₂ FN ₅ O ₂ S
315779	2-tetrazolyl-CH ₂ CH ₂	2 <i>R</i> *,5 <i>S</i> *	C ₂₀ H ₂₂ FN ₅ O ₂ S
315780	1-imidazolyl-(CH ₂) ₃	2 <i>S</i> ,5 <i>S</i>	C ₂₃ H ₂₆ FN ₃ O ₂ S
315781	4,6-(Me)2-2-pyrimidinyl-(CH ₂) ₃	2 <i>R</i> *,5 <i>R</i> *	C ₂₆ H ₃₀ FN ₃ O ₂ S
315782	1,3,4-oxadiazol-2-yl	2 <i>R</i> *,5 <i>S</i> *	C ₁₉ H ₁₈ FN ₃ O ₃ S
315783	2-tetrazolyl-(CH ₂) ₄	2 <i>R</i> *,5 <i>R</i> *	C ₂₂ H ₂₆ FN ₅ O ₂ S



315777: C20 H24 F N O3 S



315778: C18 H26 N2 O3 S

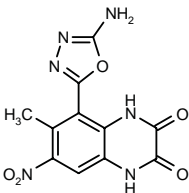
SOURCE – Roche.

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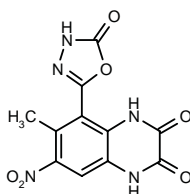
315794

5-(5-Amino-1,3,4-oxadiazol-2-yl)-6-methyl-7-nitro-1,2,3,4-tetrahydroquinoxaline-2,3-dione



C11 H8 N6 O5; Mol wt: 304.2212

ACTION – Glutamate antagonist with *in vitro* activity against AMPA receptors and the glycine site of NMDA receptors. Potentially useful for the treatment of cerebral ischemia, chronic neurodegenerative disorders including Alzheimer’s disease, Parkinson’s disease and Huntington’s disease, seizure disorders, schizophrenia, anxiety, pain and drug abuse. Another exemplified quinoxaline-2,3-dione derivative is:



315795: C11 H7 N5 O6

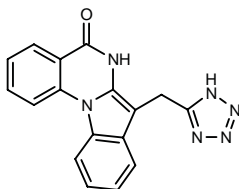
SOURCE – Pfizer.

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1. Kornberg, B.E. et al. (Pfizer Inc.) *Conformationally semi-constrained quinoxaline 2,3-diones as neuroprotective agents*. US 6340758.

316105

7-(1*H*-Tetrazol-5-ylmethyl)indolo[1,2-*a*]quinazolin-5(6*H*)-one



C17 H12 N6 O; Mol wt: 316.3228

ACTION – A specifically claimed compound from a group of indolo[1,2-*a*]quinazolin-5-one derivatives effective as a poly(ADP-ribose) polymerase (PARP, NAD⁺ ADP-ribosyltransferase) inhibitors. Potentially useful for the treatment of a broad range of conditions including apoptosis, neural tissue damage resulting from ischemia–reperfusion injury, neurological and neurodegenerative disorders such as Alzheimer’s disease, Parkinson’s disease, multiple sclerosis, etc., vascular stroke, cardiovascular disorders including myocardial infarction and unstable angina, age-related macular degeneration, AIDS, arthritis, atherosclerosis, cachexia, cancer, diabetes, head and spinal cord trauma, immune senescence, inflammatory bowel disorders, osteoporosis, pain, renal failure, retinal ischemia, septic shock and skin aging.

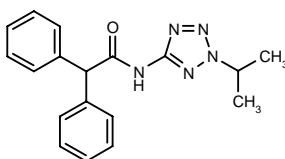
SOURCE – Novartis.

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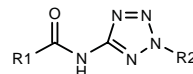
316188

N-(2-Isopropyl-2*H*-tetrazol-5-yl)-2,2-diphenylacetamide



C18 H19 N5 O; Mol wt: 321.3821

ACTION – Metabotropic glutamate receptor agonist giving an EC₅₀ of 0.100 μM using rat mglu_{1a} receptors expressed in EBNA cells. Potentially useful for the treatment of acute and chronic neurological disorders such as restricted brain function caused by bypass operations or transplant, poor blood supply to the brain, head and spinal cord trauma, hypoxia caused by pregnancy, cardiac arrest, hypoglycemia, Alzheimer’s disease, Huntington’s chorea, amyotrophic lateral sclerosis, AIDS dementia, eye injuries, retinopathy, cognitive disorders, memory deficits, schizophrenia and idiopathic or medicament-related parkinsonism. Other exemplified tetrazole derivatives are:



Compound	R1	R2	Formula
316189	CH(Ph) ₂	Me	C ₁₆ H ₁₅ N ₅ O
316192	9H-xanthen-9-yl	Me	C ₁₆ H ₁₃ N ₅ O ₂
316196	9H-xanthen-9-yl	i-Pr	C ₁₈ H ₁₇ N ₅ O ₂
316197	CH(Ph) ₂	CH ₂ CF ₃	C ₁₇ H ₁₄ F ₃ N ₅ O
316198	9H-xanthen-9-yl	CH ₂ CF ₃	C ₁₇ H ₁₂ F ₃ N ₅ O ₂
316199	6,11-dihydrodibenzo[b,e]oxepin-11-yl	Et	C ₁₈ H ₁₇ N ₅ O ₂
316200	9-thioxanthenyl	Et	C ₁₇ H ₁₅ N ₅ OS
316202	2-MeO-9-xanthenyl	Et	C ₁₈ H ₁₇ N ₅ O ₃

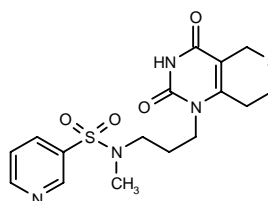
SOURCE – Roche.

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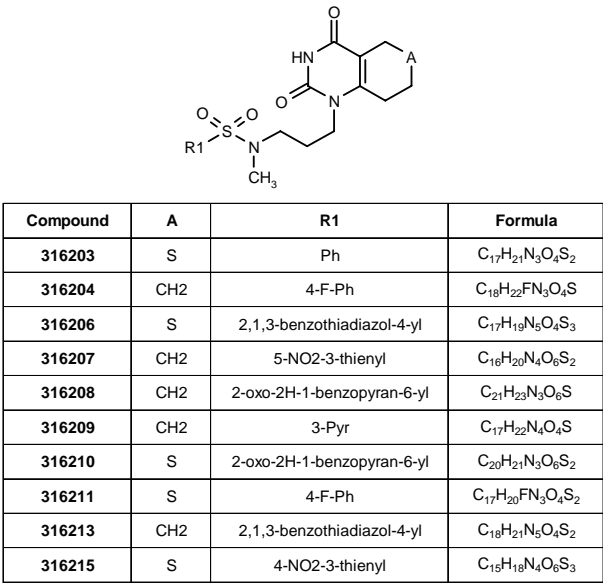
316201

N-[3-(2,4-Dioxo-2,3,4,5,7,8-hexahydro-1*H*-thiopyrano-[4,3-*d*]pyrimidin-1-yl)propyl]-*N*-methylpyridine-3-sulfonamide



C16 H20 N4 O4 S2; Mol wt: 396.4900

ACTION – A poly(ADP-ribose)polymerase (PARP, NAD⁺ ADP-ribosyltransferase) inhibitor that displayed an IC₅₀ of 0.04 μM against PARP, and was shown to protect endothelial cells from H₂O₂-induced toxicity with an IC₅₀ of 0.25 μM. Potentially useful for the treatment of ischemia–reperfusion injury. Other exemplified uracil derivatives are:



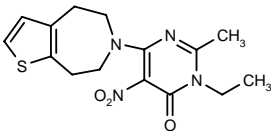
SOURCE – Bayer.

REFERENCES

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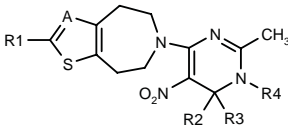
316218

3-Ethyl-2-methyl-5-nitro-6-(5,6,7,8-tetrahydro-4H-thieno[2,3-d]azepin-6-yl)pyrimidin-4(3H)-one



C15 H18 N4 O3 S; Mol wt: 334.3982

ACTION – An antagonist of group I metabotropic glutamate receptors giving an IC₅₀ of 0.069 μM at mglu_{1a} receptors expressed in HEK 293 cells. Potentially useful for the treatment of epilepsy, stroke, chronic and acute pain, psychosis, schizophrenia, Alzheimer's disease, cognitive disorders, memory deficits, restricted brain function caused by bypass operations or transplant, poor blood supply to the brain, head and spinal cord trauma, hypoxia caused by pregnancy, cardiac arrest, hypoglycemia, Huntington's chorea, amyotrophic lateral sclerosis, AIDS dementia, eye injuries, retinopathy and idiopathic or medicament-related parkinsonism. Other heterocycloazepinyl-substituted pyrimidines include the following:



Compound	R1	R2	R3	R4	A	Formula
316220	Me	-O-		H	N	C ₁₃ H ₁₅ N ₅ O ₃ S
316222	Me	OEt		bond	N	C ₁₅ H ₁₉ N ₅ O ₃ S
316223	Me	-O-		Et	N	C ₁₅ H ₁₉ N ₅ O ₃ S
316225	NH2	-O-		H	N	C ₁₂ H ₁₄ N ₆ O ₃ S
316227	NH2	-O-		Et	N	C ₁₄ H ₁₈ N ₆ O ₃ S
316230	H	-O-		H	N	C ₁₂ H ₁₃ N ₅ O ₃ S
316236	H	-O-		H	CH	C ₁₃ H ₁₄ N ₄ O ₃ S
316237	H	OEt		bond	CH	C ₁₅ H ₁₈ N ₄ O ₃ S

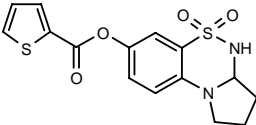
SOURCE – Roche.

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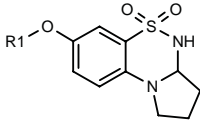
316291

Thiophene-2-carboxylic acid 5,5-dioxo-2,3,3a,4-tetrahydro-1H-pyrrolo[2,1-c][1,2,4]benzothiadiazin-7-yl ester



C15 H14 N2 O4 S2; Mol wt: 350.4176

ACTION – AMPA receptor modulator proven to increase the AMPA-induced current by 100% in voltage-clamp experiments at 1.3 μM in rat cortical preparations. Potentially useful for the treatment of cognitive disorders associated with age, anxiety, depression, Alzheimer's disease, Pick's disease, Huntington's chorea, schizophrenia, acute and progressive neurodegenerative diseases, ischemia and epilepsy. Other specifically claimed benzothiadiazine derivatives are:



Compound	R1	Formula
316298	H	C ₁₀ H ₁₂ N ₂ O ₃ S
316301	COPh	C ₁₇ H ₁₆ N ₂ O ₄ S
316303	cyclohexyl-CO	C ₁₇ H ₂₂ N ₂ O ₄ S
316306	cyclobutyl-CO	C ₁₅ H ₁₈ N ₂ O ₄ S
316309	4-Me-PhCO	C ₁₈ H ₁₈ N ₂ O ₄ S
316310	3-thienyl-CO	C ₁₅ H ₁₄ N ₂ O ₅ S ₂
316311	3-furyl-CO	C ₁₅ H ₁₄ N ₂ O ₅ S
316312	2-furyl-CO	C ₁₅ H ₁₄ N ₂ O ₅ S
316313	3-Pyr-CO	C ₁₆ H ₁₆ N ₃ O ₄ S

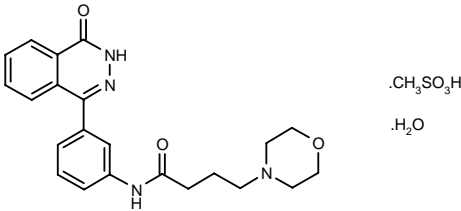
SOURCE – Servier.

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316986

4-(4-Morpholinyl)-*N*-[3-(4-oxo-3,4-dihydrophthalazin-1-yl)-phenyl]butyramide methanesulfonate hydrate



C22 H24 N4 O3 . C H4 O3 S . H2O; Mol wt: 506.5770

ACTION – An inhibitor of PARP (poly[ADP-ribose] polymerase, NAD⁺ ADP-ribosyltransferase), giving an IC₅₀ of 42 nM. Potentially useful for the treatment or prevention of ischemic disorders, inflammatory diseases, neurodegenerative diseases, diabetes, shock, head trauma, renal insufficiency and hyperalgesia.

SOURCE – Ono.

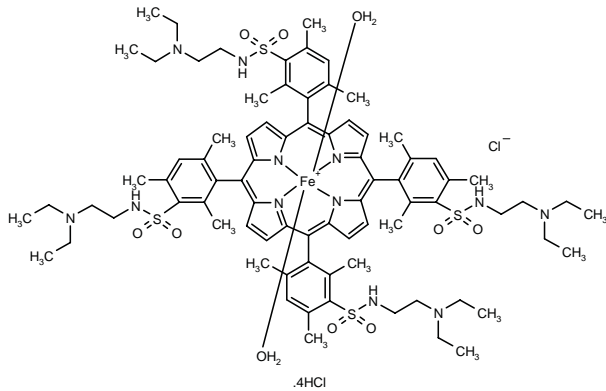
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EUK-401

315677

Diaqua[[3,3',3'',3'''-(21*H*,23*H*-porphine-5,10,15,20-tetrayl-κ*N*²¹,κ*N*²²,κ*N*²³,κ*N*²⁴)tetrakis[*N*-[2-(diethylamino)ethyl]-2,4,6-trimethylbenzenesulfonamido]](2-)]iron(1+) chloride tetrahydrochloride



C80 H108 Cl Fe N12 O8 S4 . 4HCl . 2H2O; Mol wt: 1767.2440

ACTION – A nongenotoxic porphyrin derivative effective as a reactive oxygen species (ROS) catalytic scavenger by virtue of its superoxide dismutase (SOD), catalase and/or peroxidase activity. It demonstrated efficacy in a mouse model of delayed-type hypersensitivity, reducing edema following topical application to oxazolone-challenged mice. Potentially useful for the treatment of ROS-mediated conditions including stroke, Alzheimer's disease, dementia, Parkinson's disease, amyotrophic lateral sclerosis, Huntington's disease, cancer, multiple sclerosis, systemic lupus erythematosus, scleroderma, eczema, dermatitis, delayed-type hypersensitivity, psoriasis, gingivitis, adult respiratory distress syndrome, septic shock, multiple organ failure, inflammation, asthma, allergic rhinitis, pneumonia, emphysema, etc.

SOURCE – Eukarion.

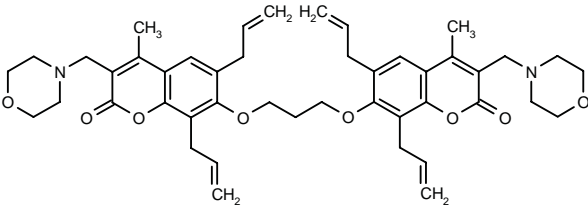
REFERENCES

1. Meunier, B. and Cosledan, F. (Eukarion, Inc.) *Non-genotoxic metalloporphyrins as synthetic catalytic scavenger of reactive oxygen species.* WO 0204454.

FID-203152

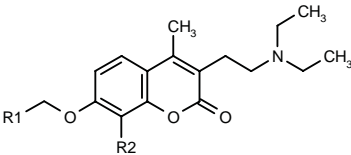
316838

7,7'-(Propylene-1,3-diyl)bis(oxy)bis[6,8-diallyl-4-methyl-3-(morpholin-4-ylmethyl)-2*H*-1-benzopyran-2-one]

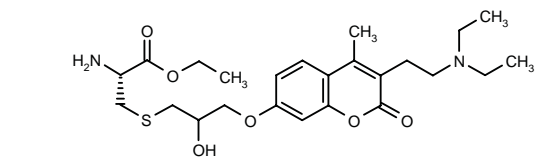


C45 H54 N2 O8; Mol wt: 750.9276

ACTION – A coumarin derivative that inhibits the release of proinflammatory cytokines, as demonstrated in rats by 72 and 64% inhibition, respectively, of TNF and IL-1β release after lipopolysaccharide (LPS) stimulation at 0.5 mg/kg i.v., and by 73 and 60% inhibition, respectively, at 2 mg/kg i.v. In the carrageenan-induced mouse paw edema model, it produced a 90% reduction in paw weight at 2 mg/kg i.v. No mortality was observed following a dose of 200 mg/kg and the maximum tolerated dose was 50 mg/kg. Potentially useful for the treatment of peripheral and cerebral vasculopathies, angina, peripheral ischemia, ischemia of organs, thrombosis and hypertension. Other exemplified compounds are:



Compound	R1	R2	Formula
FID-201273 [316841]	CH(OH)Bu	H	C ₂₂ H ₃₃ NO ₄
FID-301326 [316843]	CH(OH)Bu	Cl	C ₂₂ H ₃₂ ClNO ₄
FID-201330 [316846]	cyclohexyl-NHCO	Cl	C ₂₄ H ₃₃ ClN ₂ O ₄



FID-201261 [316839]: C24 H36 N2 O6 S

SOURCE – Fidia.

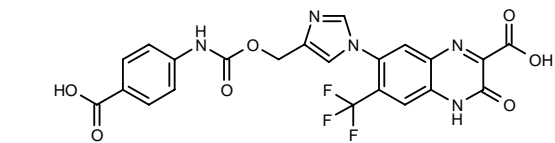
REFERENCES

1. Prosdocimi, M. et al. (Fidia SpA) *Novel coumarin derivs. and the salts thereof, a process for the preparation thereof and their use in the pharmaceutical field.* WO 0210148.

KRP-199*

275908

7-[4-[N-(4-Carboxyphenyl)carbamoyloxymethyl]-1 H-imidazol-1-yl]-3-oxo-6-(trifluoromethyl)-3,4-dihydroquinoxaline-2-carboxylic acid



C22 H14 F3 N5 O7; Mol wt: 517.3746

ACTION – Quinoxalinecarboxylic acid derivative with strong and selective AMPA receptor-antagonist activity and excellent aqueous solubility. Potentially useful for the treatment of stroke.

SOURCE – Kyorin.

REFERENCES

1. Takano, Y. et al. (Kyorin Pharmaceutical Co., Ltd.) *6,7-Asymmetrically disubstd. quinoxalinecarboxylic acid derivs., addition salts thereof, and processes for the preparation of both.* EP 1020453, JP 2000080085, US 6348461, WO 9911632.

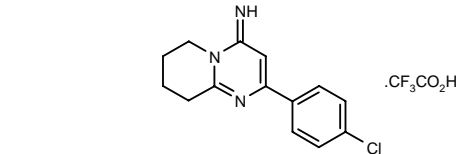
2. Takano, Y. et al. *Discovery of KRP-199: Synthesis of novel quinoxalinecarboxylic acid derivatives as highly potent and selective AMPA receptor antagonists.* 223rd ACS Natl Meet (April 7-11, Orlando) 2002, Abst MEDI 42.

*Identified compound **275908** (see **275907**) Drug Data Rep 1999, 021(08): 0684.

L-452493-001X

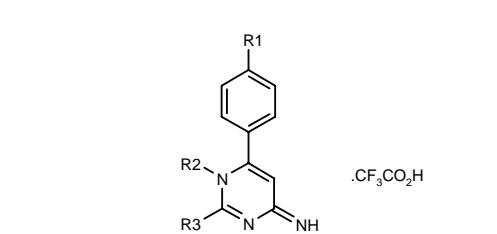
315309

2-(4-Chlorophenyl)-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]-pyrimidin-4-imine trifluoroacetate

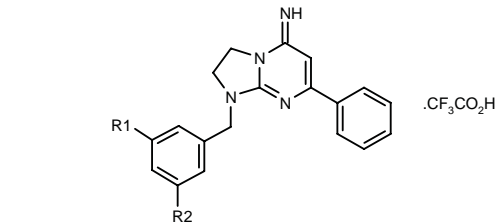


C14 H14 Cl N3 . C2 H F3 O2; Mol wt: 373.7605

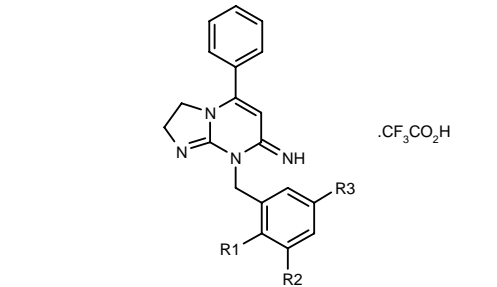
ACTION – An NMDA antagonist targeting the NR2B subunit of the receptor, potentially useful for the treatment of pain, migraine, depression, anxiety, schizophrenia, Parkinson's disease and stroke. Other exemplified 4-iminopyrimidine compounds are:



Compound	R1	R2,R3	Formula
L-453449-001G [315310]	OMe	-(CH2)4-	C15H17N3O .C2HF3O2
L-425037-001E [315311]	H	-CH2CH2N(CH2Ph)-	C19H18N4 .C2HF3O2
L-426021-001E [315320]	H	-CH=CHN[3,5-(Me)2-PhCH2]-	C21H20N4 .C2HF3O2
L-426022-001N [315321]	H	-CH=CHN(CH2Ph)-	C19H18N4 .C2HF3O2
L-426023-001X [315323]	H	-CH=CHN(CH2CH2Ph)-	C20H18N4 .C2HF3O2
L-429067-001K [315325]	H	-CH2CH2N[3,5-(Me)2-PhCH2]-	C21H22N4 .C2HF3O2



Compound	R1=R2	Formula
L-425038-001N [315313]	H	C19H18N4.C2HF3O2
L-426666-001B [315324]	Cl	C19H16Cl2N4.C2HF3O2



Compound	R1	R2	R3	Formula
L-425649-001Y [315314]	H	H	Cl	C19H17ClN4.C2HF3O2
L-425652-001E [315316]	OMe	H	H	C20H20N4O.C2HF3O2
L-425653-001N [315317]	H	H	OMe	C20H20N4O.C2HF3O2
L-425654-001X [315318]	H	Cl	Cl	C19H16Cl2N4.C2HF3O2
L-425656-001P [315319]	H	Me	Me	C21H22N4.C2HF3O2

SOURCE – Merck & Co.

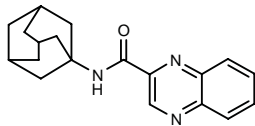
REFERENCES

1. Claremon, D.A. et al. (Merck & Co., Inc.) *Iminopyrimidine NMDA NR2B receptor antagonists.* WO 0200629.

NPS-2390

266383

N-(1-Adamantyl)quinoxaline-2-carboxamide



C19 H21 N3 O; Mol wt: 307.3949

ACTION – Potent and selective group I metabotropic glutamate receptor antagonist proven to inhibit the activation of a calcium receptor–mglu₁ receptor chimera (IC₅₀ = 5.2 nM) and a calcium receptor–mglu₅ receptor chimera (IC₅₀ = 82.0 nM). Potentially useful for the treatment of CNS disorders such as stroke and epilepsy.

SOURCE – NPS Pharmaceuticals.

REFERENCES

1. VanWagenen, B.C. et al. (NPS Pharmaceuticals, Inc.) *Metabotropic glutamate receptor antagonists for treating central nervous system diseases*. EP 1037878, JP 2001524468, WO 9926927.

2. VanWagenen, B.C. et al. *In vitro pharmacological characterizations of NPS 2390: A highly potent and selective, noncompetitive antagonist of group I metabotropic glutamate receptors*. Soc Neurosci Abst 1998, 24(Part 1): Abst 229.18.

3. VanWagenen, B.C. et al. *Structure-activity relationship studies of group I metabotropic glutamate receptor antagonists*. 223rd ACS Natl Meet (April 7-11, Orlando) 2002, Abst MEDI 151.

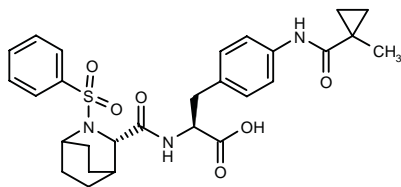
4. VanWagenen, B.C. et al. *Structure-activity relationships studies of NPS 2390: A potent and selective group I metabotropic glutamate receptor antagonist*. Soc Neurosci Abst 2000, 26(Part 2): Abst 618.3.

RESPIRATORY DRUGS

ASTHMA THERAPY

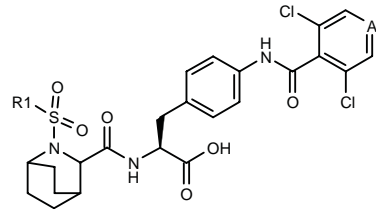
315724

4-(1-Methylcyclopropylcarboxamido)-N-[2-(phenylsulfonyl)-2-azabicyclo[2.2.2]oct-3(S)-ylcarbonyl]-L-phenylalanine



C28 H33 N3 O6 S; Mol wt: 539.6497

ACTION – Cell adhesion inhibitor that acts as an antagonist at $\alpha_4\beta_1$ (VLA-4) receptors, as demonstrated by its ability to inhibit the adhesion of Ramos cells to VCAM-1-coated plates (IC₅₀ = 4 nM). Potentially useful for the treatment of asthma, bronchoconstriction, restenosis, atherosclerosis, irritable bowel syndrome and multiple sclerosis, as well as other inflammatory, autoimmune and proliferative disorders including psoriasis, rheumatoid arthritis, inflammatory bowel syndrome or transplant rejection. Other exemplified compounds are:



Compound	R1	A	Isomer	Formula
315725	Ph	N	S	C ₂₉ H ₂₈ Cl ₂ N ₄ O ₆ S
315727	2-thienyl	CH		C ₂₈ H ₂₇ Cl ₂ N ₃ O ₆ S ₂
315728	2-thienyl	N		C ₂₇ H ₂₆ Cl ₂ N ₄ O ₆ S ₂

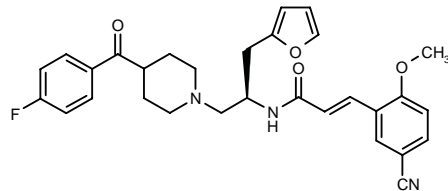
SOURCE – Ortho-McNeil.

REFERENCES

1. Dyatkin, A.B. et al. (Ortho-McNeil Pharmaceutical, Inc.) *Aza-bridged-bicyclic amino acid derivs. as alpha4 integrin antagonists*. WO 0202556.

315979

3-(5-Cyano-2-methoxyphenyl)-N-[2-[4-(4-fluorobenzoyl)piperidin-1-yl]-1-(R)-(furan-2-ylmethyl)ethyl]-2-propenamide



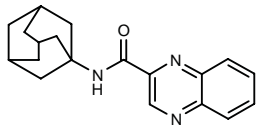
C30 H30 F N3 O4; Mol wt: 515.5820

ACTION – Chemokine CCR3 receptor antagonist proven to inhibit [¹²⁵I]-human eotaxin binding to CCR3 receptors expressed in RBL-2H3 cells with an IC₅₀ of 2 nM; it exhibited 36-fold selectivity over α_1 -adrenoceptors in rat cerebral cortex preparations. Potentially useful for the treatment of inflammatory and allergic conditions, particularly inflammatory or obstructive airways diseases. Other exemplified piperidine compounds are:

NPS-2390

266383

N-(1-Adamantyl)quinoxaline-2-carboxamide



C19 H21 N3 O; Mol wt: 307.3949

ACTION – Potent and selective group I metabotropic glutamate receptor antagonist proven to inhibit the activation of a calcium receptor–mglu₁ receptor chimera (IC₅₀ = 5.2 nM) and a calcium receptor–mglu₅ receptor chimera (IC₅₀ = 82.0 nM). Potentially useful for the treatment of CNS disorders such as stroke and epilepsy.

SOURCE – NPS Pharmaceuticals.

REFERENCES

1. VanWagenen, B.C. et al. (NPS Pharmaceuticals, Inc.) *Metabotropic glutamate receptor antagonists for treating central nervous system diseases*. EP 1037878, JP 2001524468, WO 9926927.

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3. VanWagenen, B.C. et al. *Structure-activity relationship studies of group I metabotropic glutamate receptor antagonists*. 223rd ACS Natl Meet (April 7-11, Orlando) 2002, Abst MEDI 151.

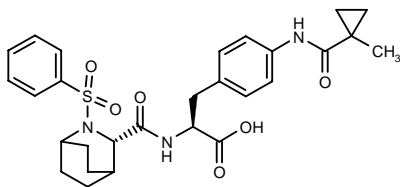
4. VanWagenen, B.C. et al. *Structure-activity relationships studies of NPS 2390: A potent and selective group I metabotropic glutamate receptor antagonist*. Soc Neurosci Abst 2000, 26(Part 2): Abst 618.3.

RESPIRATORY DRUGS

ASTHMA THERAPY

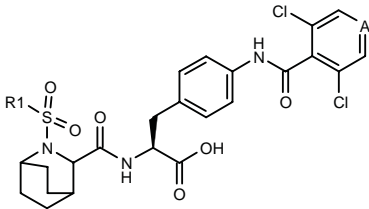
315724

4-(1-Methylcyclopropylcarboxamido)-N-[2-(phenylsulfonyl)-2-azabicyclo[2.2.2]oct-3(S)-ylcarbonyl]-L-phenylalanine



C28 H33 N3 O6 S; Mol wt: 539.6497

ACTION – Cell adhesion inhibitor that acts as an antagonist at $\alpha_4\beta_1$ (VLA-4) receptors, as demonstrated by its ability to inhibit the adhesion of Ramos cells to VCAM-1-coated plates (IC₅₀ = 4 nM). Potentially useful for the treatment of asthma, bronchoconstriction, restenosis, atherosclerosis, irritable bowel syndrome and multiple sclerosis, as well as other inflammatory, autoimmune and proliferative disorders including psoriasis, rheumatoid arthritis, inflammatory bowel syndrome or transplant rejection. Other exemplified compounds are:



Compound	R1	A	Isomer	Formula
315725	Ph	N	S	C ₂₉ H ₂₈ Cl ₂ N ₄ O ₆ S
315727	2-thienyl	CH		C ₂₈ H ₂₇ Cl ₂ N ₃ O ₆ S ₂
315728	2-thienyl	N		C ₂₇ H ₂₆ Cl ₂ N ₄ O ₆ S ₂

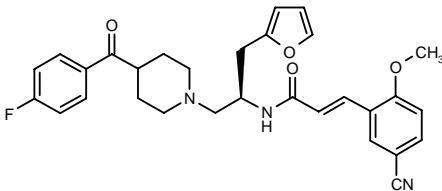
SOURCE – Ortho-McNeil.

REFERENCES

1. Dyatkin, A.B. et al. (Ortho-McNeil Pharmaceutical, Inc.) *Aza-bridged-bicyclic amino acid derivs. as alpha4 integrin antagonists*. WO 0202556.

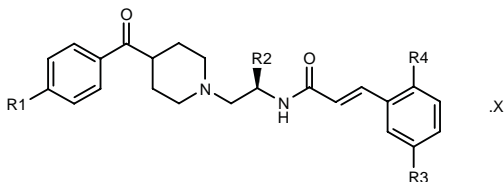
315979

3-(5-Cyano-2-methoxyphenyl)-N-[2-[4-(4-fluorobenzoyl)piperidin-1-yl]-1-(R)-(furan-2-ylmethyl)ethyl]-2-propenamide



C30 H30 F N3 O4; Mol wt: 515.5820

ACTION – Chemokine CCR3 receptor antagonist proven to inhibit [¹²⁵I]-human eotaxin binding to CCR3 receptors expressed in RBL-2H3 cells with an IC₅₀ of 2 nM; it exhibited 36-fold selectivity over α_1 -adrenoceptors in rat cerebral cortex preparations. Potentially useful for the treatment of inflammatory and allergic conditions, particularly inflammatory or obstructive airways diseases. Other exemplified piperidine compounds are:



Compound	R1	R2	R3	R4	X	Formula
315980	F	H	CN	H	CF3CO2H	C ₂₄ H ₂₄ FN ₃ O ₂ .C ₂ HF ₃ O ₂
315981	F	CH2Ph	CN	H		C ₃₁ H ₃₀ FN ₃ O ₂
315982	F	CH2Ph	Br	OEt		C ₃₂ H ₃₄ BrFN ₂ O ₃
315983	F	3-Pyr-CH2	Br	OMe		C ₃₀ H ₃₁ BrFN ₃ O ₃
315984	Cl	H	Br	OMe	CF3CO2H	C ₂₄ H ₂₆ BrClN ₂ O ₃ .C ₂ HF ₃ O ₂
315985	F	H	Br	i-PrO	CF3CO2H	C ₂₆ H ₃₀ BrFN ₂ O ₃ .C ₂ HF ₃ O ₂
315987	F	2-furyl-CH2	CN	H		C ₂₉ H ₂₈ FN ₃ O ₃
315988	F	CH2OH	Br	OMe		C ₂₅ H ₂₈ BrFN ₂ O ₄
315989	F	H	Br	OMe	CF3CO2H	C ₂₄ H ₂₆ BrFN ₂ O ₃ .C ₂ HF ₃ O ₂
315990	F	5-imidazolyl-CH2	CN	OMe		C ₂₉ H ₃₀ FN ₅ O ₃
315991	Cl	CH2OH	Cl	OMe	CF3CO2H	C ₂₅ H ₂₈ Cl ₂ N ₂ O ₄ .C ₂ HF ₃ O ₂
315992	Cl	CH2OH	Br	OMe		C ₂₅ H ₂₈ BrClN ₂ O ₄
315993	F	4-Pyr-CH2	CN	OMe		C ₃₁ H ₃₁ FN ₄ O ₃

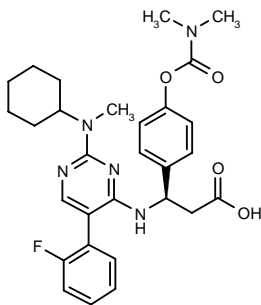
SOURCE – Novartis.

REFERENCES

1. Howe, T.J. et al. (Novartis AG;Novartis-Erfindungen VmbH) *Piperidine cpds. for use as CCR-3 inhibitors*. WO 0204420.

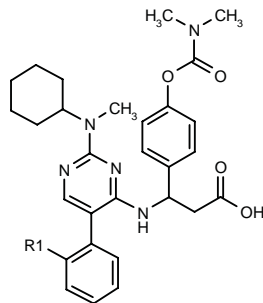
316704

3(*R*)-[2-(*N*-Cyclohexyl-*N*-methylamino)-5-(2-fluorophenyl)pyrimidin-4-ylamino]-3-[4-(*N,N*-dimethylcarbamoyloxyphenyl)propionic acid



C₂₉ H₃₄ F N₅ O₄; Mol wt: 535.6166

ACTION – Agent with the ability to inhibit VLA-4-mediated leukocyte adhesion, potentially useful for the treatment of asthma, Alzheimer's disease, atherosclerosis, AIDS dementia, diabetes, inflammatory bowel disease, multiple sclerosis, rheumatoid arthritis, transplant rejection, cancer, meningitis, encephalitis, stroke, brain trauma, nephritis, retinitis, atopic dermatitis, psoriasis, myocardial ischemia, adult respiratory distress syndrome, etc. Other exemplified β -amino acid derivatives include the following:



Compound	R1	Isomer	Formula
316705	F	S	C ₂₈ H ₃₄ FN ₅ O ₄
316707	Me		C ₃₀ H ₃₇ N ₅ O ₄

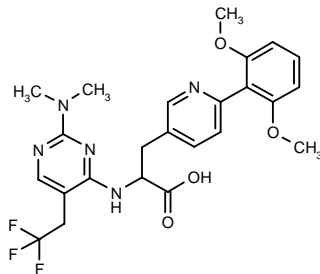
SOURCES – Elan; Wyeth.

REFERENCES

1. Konradi, A.W. et al. (Elan Pharmaceuticals, Inc.; American Home Products Corp.) *β -Amino acid derivs.-inhibitors of leukocyte adhesion mediated by VLA-4*. WO 0208201.

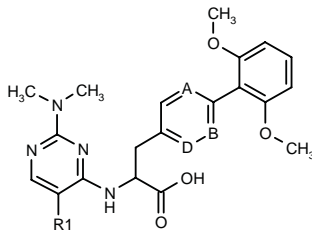
316716

3-[6-(2,6-Dimethoxyphenyl)pyridin-3-yl]-*N*-[2-(dimethylamino)-5-(2,2,2-trifluoroethyl)pyrimidin-4-yl]-DL-alanine



C24 H26 F3 N5 O4; Mol wt: 505.4944

ACTION – Agent with the ability to inhibit VLA-4-mediated leukocyte adhesion, potentially useful for the treatment of asthma, Alzheimer's disease, atherosclerosis, AIDS dementia, diabetes, inflammatory bowel disease, multiple sclerosis, rheumatoid arthritis, transplant rejection, cancer, meningitis, encephalitis, stroke, brain trauma, nephritis, retinitis, atopic dermatitis, psoriasis, myocardial ischemia, adult respiratory distress syndrome, etc. Other exemplified alanine derivatives include the following:



Compound	R1	A	B	D	Formula
316719	CH ₂ CF ₃	N	N	CH	C ₂₃ H ₂₅ F ₃ N ₆ O ₄
316720	i-Pr	CH	CH	N	C ₂₅ H ₃₁ N ₅ O ₄
316721	i-Pr	N	CH	N	C ₂₄ H ₃₀ N ₆ O ₄
316722	CH(Et) ₂	N	N	CH	C ₂₆ H ₃₄ N ₆ O ₄
316723	3,5-(Me) ₂ -4-isoxazolyl	CH	CH	N	C ₂₇ H ₃₀ N ₆ O ₅
316724	1,3,5-(Me) ₃ -4-pyrazolyl	CH	CH	N	C ₂₈ H ₃₃ N ₇ O ₄
316725	3,5-(Me) ₂ -4-isothiazolyl	N	CH	N	C ₂₆ H ₂₉ N ₇ O ₄ S

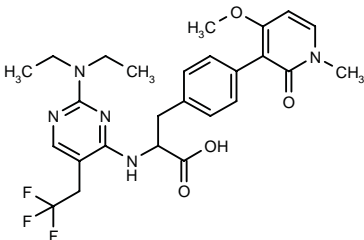
SOURCES – Elan; Wyeth.

REFERENCES

1. Konradi, A.W. et al. (Elan Pharmaceuticals, Inc.;American Home Products Corp.) 3-(Heteroaryl)alanine derivs.-inhibitors of leukocyte adhesion mediated by VLA-4. WO 0208203.

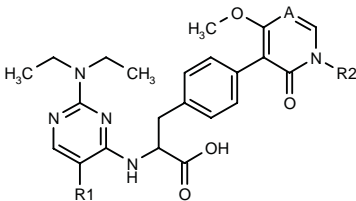
316735

N-[2-(Diethylamino)-5-(2,2,2-trifluoroethyl)pyrimidin-4-yl]-4-(4-methoxy-1-methyl-2-oxo-1,2-dihydropyridin-3-yl)-DL-phenylalanine



C26 H30 F3 N5 O4; Mol wt: 533.5480

ACTION – Agent with the ability to inhibit VLA-4-mediated leukocyte adhesion, potentially useful for the treatment of asthma, Alzheimer’s disease, atherosclerosis, AIDS dementia, diabetes, inflammatory bowel disease, multiple sclerosis, rheumatoid arthritis, transplant rejection, cancer, meningitis, encephalitis, stroke, brain trauma, nephritis, retinitis, atopic dermatitis, psoriasis, myocardial ischemia, adult respiratory distress syndrome, etc. Other exemplified α-amino acid derivatives include the following:



Compound	R1	R2	A	Formula
316745	CH2CF3	Pr	N	C ₂₇ H ₃₃ F ₃ N ₆ O ₄
316747	i-Pr	Et	N	C ₂₇ H ₃₆ N ₆ O ₄
316748	CH(Et)2	Me	N	C ₂₈ H ₃₈ N ₆ O ₄
316749	3,5-(Me)2-4-isoxazolyl	i-Pr	CH	C ₃₁ H ₃₈ N ₆ O ₅
316750	1,3,5-(Me)3-4-pyrazolyl	Pr	CH	C ₃₂ H ₄₁ N ₇ O ₄
316751	3,5-(Me)2-4-isothiazolyl	Et	CH	C ₃₀ H ₃₆ N ₆ O ₄ S
316752	3,5-(Me)2-4-isothiazolyl	i-Pr	N	C ₃₀ H ₃₇ N ₇ O ₄ S

SOURCES – Elan; Wyeth.

REFERENCES

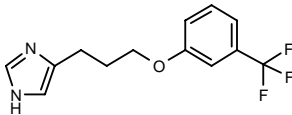
1. Konradi, A.W. et al. (Elan Pharmaceuticals, Inc.; American Home Products Corp.) α-Amino acid derivs.-inhibitors of leukocyte adhesion mediated by VLA-4. WO 0208202.

TRIFLUPROXIM*

242742

4-[3-[3-(Trifluoromethyl)phenoxy]propyl]-1H-imidazole

UCL-1470



C13 H13 F3 N2 O; Mol wt: 270.2570

ACTION – Potent full agonist at histamine H₃ receptors with an ED₅₀ value of 0.6 mg/kg p.o. for inhibition of brain *tele*-methylhistamine formation in mice. Potentially useful as an antiallergic and antiasthmatic agent.

SOURCES – Bioprojet; INSERM, Paris Cedex (FR).

REFERENCES

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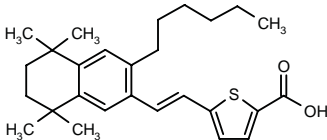
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*Identified compound 242742 Drug Data Rep 1997, 019(02): 0128.

TREATMENT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASES

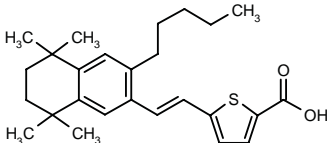
315551

5-[2-(3-Hexyl-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)vinyl]thiophene-2-carboxylic acid



C27 H36 O2 S; Mol wt: 424.6454

ACTION – A selective retinoic acid receptor RAR γ agonist able to induce alveolar repair in a rat model of elastase-induced emphysema following oral administration at doses below 0.1 mg/kg. Potentially useful for the treatment of emphysema and associated pulmonary diseases. Another specifically claimed thiophene derivative is:



315552: C26 H34 O2 S

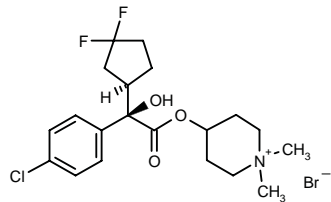
SOURCE – Roche.

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1. Klaus, M. and Lapierre, J.-M. (F. Hoffmann-La Roche AG) *Thiophene retinoids*. WO 0204439.

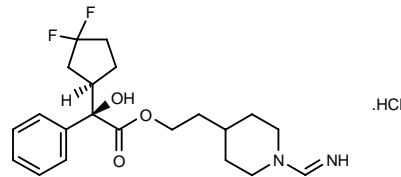
316785

4-[2(*R*)-(4-Chlorophenyl)-2-[(*R*)-3,3-difluorocyclopentyl]-2-hydroxyacetoxy]-1,1-dimethylpiperidinium bromide



C20 H27 Br Cl F2 N O3; Mol wt: 482.7903

ACTION – Muscarinic M₃ receptor antagonist that gave a K_i of 0.425 nM against M₃ receptors expressed in CHO cells, showing 68.5-fold selectivity over M₂ receptors. In a functional assay measuring carbachol-induced contractions, compound displayed a K_i of 0.044 nM against M₃ receptors and 218-fold selectivity over M₂ receptors. It was shown to inhibit methacholine-induced bronchoconstriction in anesthetized dogs. Potentially useful for the treatment of respiratory disorders including chronic obstructive pulmonary disease, chronic bronchitis, asthma, pulmonary fibrosis, pulmonary emphysema and rhinitis. Another exemplified α-hydroxy acid ester derivative is:



316791: C21 H28 F2 N2 O3 . HCl

SOURCE – Banyu.

REFERENCES

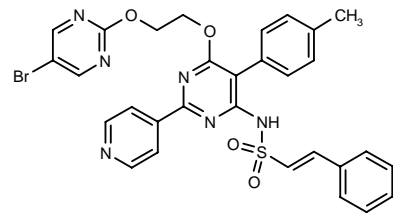
1. Ogino, Y. et al. (Banyu Pharmaceutical Co., Ltd.) *Ester derivs*. WO 0204402.

CARDIOVASCULAR DRUGS

ANTIHYPERTENSIVE DRUGS

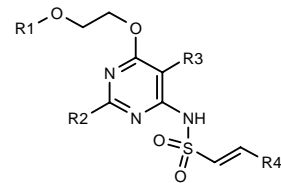
316396

N-[6-[2-(5-Bromopyrimidin-2-yloxy)ethoxy]-5-(4-methylphenyl)-2-(4-pyridyl)pyrimidin-4-yl]-2-phenylvinyl-sulfonamide



C30 H25 Br N6 O4 S; Mol wt: 645.5355

ACTION – Endothelin ET_A and ET_B receptor antagonist, displaying IC₅₀ values of 19.7 and 2569 nM, respectively, against ET_A and ET_B receptors expressed in CHO cells. Compound was also shown to inhibit ET-1-induced contractions in rat aortic rings (mediated by ET_A receptors) and sarafotoxin S6c-induced contractions in rat tracheal rings (mediated by ET_B receptors) with pA₂ values of 8.35 and 5.21, respectively. Potentially useful for the treatment of circulatory disorders including hypertension, ischemia, vasospasm and angina pectoris, as well as other endothelin-mediated conditions such as migraine, asthma and inflammatory disorders. Other exemplified sulfonamides are:



Compound	R1	R2	R3	R4	Formula
316397	5-Br-2-pyrimidinyl	H	4-Me-Ph	Ph	C ₂₆ H ₂₂ BrN ₅ O ₄ S
316398	5-Br-2-pyrimidinyl	H	4-Cl-Ph	Ph	C ₂₄ H ₁₈ BrClN ₅ O ₄ S
316399	5-Br-2-pyrimidinyl	H	4-Me-Ph	2-thienyl	C ₂₃ H ₂₀ BrN ₅ O ₄ S ₂
316401	5-Br-2-pyrimidinyl	H	4-Br-Ph	Ph	C ₂₄ H ₁₈ Br ₂ N ₅ O ₄ S
316403	2-pyrimidinyl	2-pyrimidinyl	2-MeO-PhO	Ph	C ₂₉ H ₂₅ N ₇ O ₆ S
316405	4-Br-Ph	2-pyrimidinyl	2-MeO-PhO	Ph	C ₃₁ H ₂₆ BrN ₅ O ₆ S
316407	5-Br-2-pyrimidinyl	4-morpholinyl	2-MeO-PhO	Ph	C ₂₉ H ₂₉ BrN ₆ O ₇ S
316408	2-pyrimidinyl	4-morpholinyl	2-MeO-PhO	Ph	C ₂₉ H ₃₀ N ₆ O ₇ S
316409	5-Br-2-pyrimidinyl	H	2-MeO-PhO	Ph	C ₂₈ H ₂₂ BrN ₅ O ₆ S

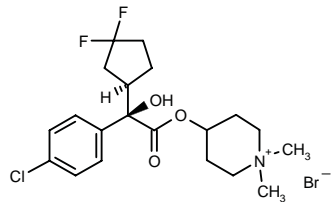
SOURCE – Roche.

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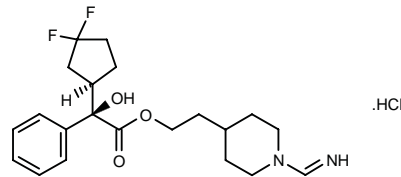
316785

4-[2(*R*)-(4-Chlorophenyl)-2-[(*R*)-3,3-difluorocyclopentyl]-2-hydroxyacetoxy]-1,1-dimethylpiperidinium bromide



C20 H27 Br Cl F2 N O3; Mol wt: 482.7903

ACTION – Muscarinic M₃ receptor antagonist that gave a K_i of 0.425 nM against M₃ receptors expressed in CHO cells, showing 68.5-fold selectivity over M₂ receptors. In a functional assay measuring carbachol-induced contractions, compound displayed a K_i of 0.044 nM against M₃ receptors and 218-fold selectivity over M₂ receptors. It was shown to inhibit methacholine-induced bronchoconstriction in anesthetized dogs. Potentially useful for the treatment of respiratory disorders including chronic obstructive pulmonary disease, chronic bronchitis, asthma, pulmonary fibrosis, pulmonary emphysema and rhinitis. Another exemplified α-hydroxy acid ester derivative is:



316791: C21 H28 F2 N2 O3 . HCl

SOURCE – Banyu.

REFERENCES

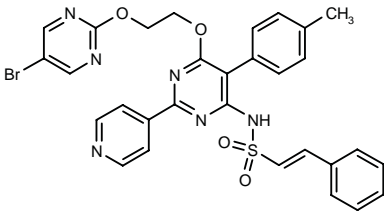
1. Ogino, Y. et al. (Banyu Pharmaceutical Co., Ltd.) *Ester derivs*. WO 0204402.

CARDIOVASCULAR DRUGS

ANTIHYPERTENSIVE DRUGS

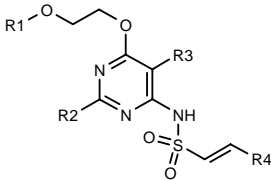
316396

N-[6-[2-(5-Bromopyrimidin-2-yloxy)ethoxy]-5-(4-methylphenyl)-2-(4-pyridyl)pyrimidin-4-yl]-2-phenylvinyl-sulfonamide



C30 H25 Br N6 O4 S; Mol wt: 645.5355

ACTION – Endothelin ET_A and ET_B receptor antagonist, displaying IC₅₀ values of 19.7 and 2569 nM, respectively, against ET_A and ET_B receptors expressed in CHO cells. Compound was also shown to inhibit ET-1-induced contractions in rat aortic rings (mediated by ET_A receptors) and sarafotoxin S6c-induced contractions in rat tracheal rings (mediated by ET_B receptors) with pA₂ values of 8.35 and 5.21, respectively. Potentially useful for the treatment of circulatory disorders including hypertension, ischemia, vasospasm and angina pectoris, as well as other endothelin-mediated conditions such as migraine, asthma and inflammatory disorders. Other exemplified sulfonamides are:



Compound	R1	R2	R3	R4	Formula
316397	5-Br-2-pyrimidinyl	H	4-Me-Ph	Ph	C ₂₆ H ₂₂ BrN ₅ O ₄ S
316398	5-Br-2-pyrimidinyl	H	4-Cl-Ph	Ph	C ₂₄ H ₁₈ BrClN ₅ O ₄ S
316399	5-Br-2-pyrimidinyl	H	4-Me-Ph	2-thienyl	C ₂₃ H ₂₀ BrN ₅ O ₄ S ₂
316401	5-Br-2-pyrimidinyl	H	4-Br-Ph	Ph	C ₂₄ H ₁₈ Br ₂ N ₅ O ₄ S
316403	2-pyrimidinyl	2-pyrimidinyl	2-MeO-PhO	Ph	C ₂₉ H ₂₅ N ₇ O ₆ S
316405	4-Br-Ph	2-pyrimidinyl	2-MeO-PhO	Ph	C ₃₁ H ₂₆ BrN ₅ O ₆ S
316407	5-Br-2-pyrimidinyl	4-morpholinyl	2-MeO-PhO	Ph	C ₂₉ H ₂₉ BrN ₆ O ₇ S
316408	2-pyrimidinyl	4-morpholinyl	2-MeO-PhO	Ph	C ₂₉ H ₃₀ N ₆ O ₇ S
316409	5-Br-2-pyrimidinyl	H	2-MeO-PhO	Ph	C ₂₈ H ₂₂ BrN ₅ O ₆ S

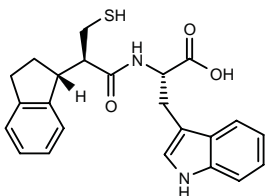
SOURCE – Actelion.

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317502

N-[2(*R*)-[1(*R*)-indanyl]-3-sulfanylpropionyl]-L-tryptophan



C23 H24 N2 O3 S; Mol wt: 408.5196

ACTION – Triple inhibitor of neutral endopeptidase (NEP; $K_i = 0.7$ nM against rabbit kidney enzyme), angiotensin-converting enzyme (ACE; $K_i = 43$ nM against rat testis enzyme) and endothelin-converting enzyme (ECE; $K_i = 26$ nM against recombinant human enzyme), potentially useful for the management of blood pressure and fluid homeostasis.

SOURCES – INSERM, Paris Cedex (FR); Servier.

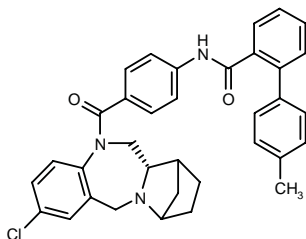
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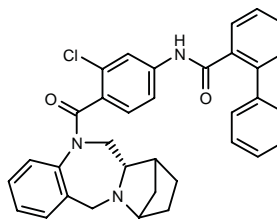
318169

N-[4-[(6a*S*)-2-Chloro-5,6,6a,7,8,9,10,12-octahydro-7,10-methanopyrido[2,1-*c*][1,4]benzodiazepin-5-ylcarbonyl]-phenyl]-4'-methylbiphenyl-2-carboxamide



C35 H32 Cl N3 O2; Mol wt: 562.1098

ACTION – Dual vasopressin V_{1a} and V_2 receptor antagonist with nanomolar affinity for these receptors ($IC_{50} = 5$ and 24 nM, respectively) and functional antagonist activity at both receptors, with respective K_i values of 13 and 23 nM. Compound reversed arginine vasopressin (AVP)-induced hypertension in rats with an ED_{50} value of 172 μ g/kg i.v. Pharmacokinetic studies in rats demonstrated an oral bioavailability of 14% and a long half-life (5 h), and it produced a significant aquaretic effect. Potentially useful in the treatment of disorders such as congestive heart failure, hypertension, renal disease, edema and hyponatremia. Another related compound is:



318166: C34 H30 Cl N3 O2

SOURCE – Johnson & Johnson.

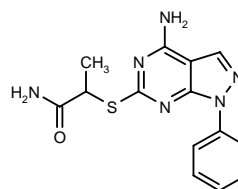
REFERENCES

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GU-285

318178

2-(4-Amino-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-ylsulfanyl)propionamide



C14 H14 N6 O S; Mol wt: 314.3716

ACTION – Potent, nonselective adenosine receptor antagonist with nanomolar affinity for both adenosine A_1 and A_{2A} receptors ($K_i = 11$ and 15 nM, respectively), proven to antagonize the functional response to the adenosine agonist *R*-PIA in spontaneously beating right atria (negative chronotropism; $pA_2 = 8.7$) and electrically paced left atria (negative inotropism; $pA_2 = 9.0$). In the potassium-arrested perfused rat heart compound antagonized only the high-sensitivity component of the biphasic coronary relaxation induced by NECA. In addition, at a dose of 1 μ mol/kg it antagonized both the chronotropic and hypotensive effects of the adenosine A_1 agonist CPA in anesthetized rats, producing a 10-fold rightward shift of the dose–response curve for the agonist. Potentially useful as an antihypertensive agent.

SOURCES – Griffith University, Queensland (AU); University of Queensland, Queensland (AU).

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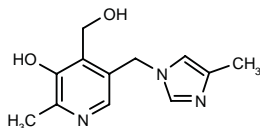
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TREATMENT OF DISORDERS OF THE CORONARY ARTERIES AND ATHEROSCLEROSIS

315554

4-(Hydroxymethyl)-2-methyl-5-(4-methyl-1*H*-imidazol-1-ylmethyl)pyridin-3-ol



C₁₂ H₁₅ N₃ O₂; Mol wt: 233.2695

ACTION – Agent with the ability to mimic the biological actions of the vitamin B₆ congeners pyridoxine and pyridoxal, proven effective in a rat model of coronary occlusion-induced myocardial infarction, reducing mortality, inducing recovery of hemodynamic parameters following occlusion, and also reducing infarct size and cardiac hypertrophy, to a similar extent as pyridoxal-5'-phosphate. Potentially useful for the treatment of cardio- and cerebrovascular disorders such as cerebral ischemia, cerebral hemorrhage, ischemic and hemorrhagic stroke, hypertension, myocardial infarction, ischemia–reperfusion injury, myocardial ischemia, congestive heart failure, arrhythmia, cardiac hypertrophy, deep venous thrombosis, disseminated intravascular coagulopathy, pulmonary embolism and platelet aggregation.

SOURCE – Medisure.

REFERENCES

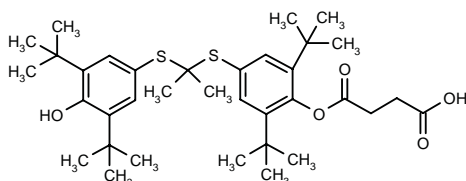
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AGI-1067

260330

Succinic acid 2,6-di-*tert*-butyl-4-[1-(3,5-di-*tert*-butyl-4-hydroxyphenyl)sulfanyl]-1-methylethylsulfanyl]phenyl monoester

AGZ-1067



C₃₅ H₅₂ O₅ S₂; Mol wt: 616.9228

ACTION – Lipophilic vascular protectant with antioxidant and lipid-lowering activity, proven to selectively inhibit the cytokine-induced expression of VCAM-1 (vascular cell adhesion molecule-1; IC₅₀ = 6 μM) and MCP-1 (monocyte chemoattractant protein-1; IC₅₀ = 10 μM) on endothelial cells. Compound lowered plasma LDL cholesterol in cholesterol-fed mice but not in LDL receptor knockout mice, where it inhibited the progression of atherosclerosis by 43, 51 and 66% in the arch, thoracic and abdominal regions, respectively. Phase II clinical studies in postangioplasty patients showed that compound (70, 140 or 280 mg once daily) for 2 weeks prior to and 4 weeks following percutaneous coronary interventions (PCI) significantly and dose-dependently improved minimal lumen dimension after PCI; rates of angiographic restenosis in stented arteries were reduced by 31%. Potentially useful for the treatment of restenosis and atherosclerosis.

SOURCE – AtheroGenics.

REFERENCES

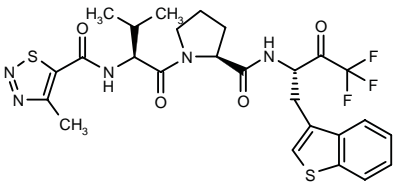
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BL-4027

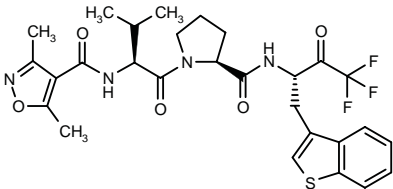
317878

N-(4-Methyl-1,2,3-thiadiazol-5-ylcarbonyl)-L-valyl-L-proline 1(*S*)-(1-benzothien-3-ylmethyl)-3,3,3-trifluoro-2-oxopropylamide



C26 H28 F3 N5 O4 S2; Mol wt: 595.6642

ACTION – Human chymase inhibitor (IC₅₀ = 36 nM) with 10-fold selectivity over human chymotrypsin (IC₅₀ = 352 nM) and good metabolic stability after oral administration in mice. Compound (100 mg/kg p.o.) exhibited *in vivo* inhibitory activity on the chymase-induced increase in vascular permeability in guinea pig skin. Potentially useful for the treatment of cardiovascular diseases and inflammation. Another related compound is:



BL-3875 [317877]: C28 H33 F3 N4 O5 S

SOURCE – Dainippon Pharmaceutical.

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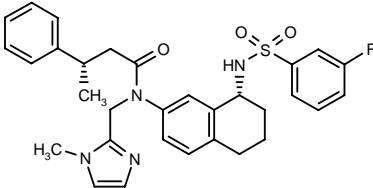
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ANTIARRHYTHMIC DRUGS

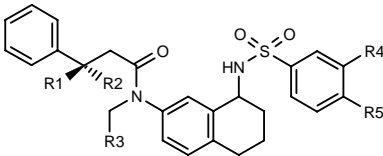
316553

N-[8(*R*)-(3-Fluorophenylsulfonamido)-5,6,7,8-tetrahydronaphthalen-2-yl]-*N*-(1-methyl-1*H*-imidazol-2-ylmethyl)-3(*S*)-phenylbutyramide



C31 H33 F N4 O3 S; Mol wt: 560.6907

ACTION – Voltage-dependent potassium Kv1.5 channel blocker found to produce 100% inhibition of potassium currents in CHO cells stably expressing the Kv1.5 potassium channel at 0.1 μM. Compound has a slow off-rate, as demonstrated by a peak current inhibition of 88%. Potentially useful for the treatment of cardiac arrhythmia. Other exemplified compounds are:



Compound	R1	R2	R3	R4	R5	Isomer	Formula
316554	Me	H	1-Me-2-imidazolyl	Cl	H	S	C ₃₁ H ₃₃ ClN ₄ O ₃ S
316555	Me	H	1-Me-2-imidazolyl	Cl	F	S	C ₃₁ H ₃₂ ClFN ₄ O ₃ S
316556	H	Me	1-Me-2-imidazolyl	H	H	R	C ₃₁ H ₃₄ N ₄ O ₃ S
316557	H	Me	1-Me-2-imidazolyl	Cl	H	R	C ₃₁ H ₃₃ ClN ₄ O ₃ S
316558	Me	H	6-Me-2-Pyr	H	H	S	C ₃₃ H ₃₆ N ₃ O ₃ S

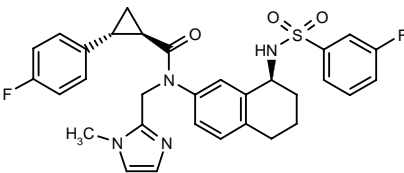
SOURCE – ICAGEN.

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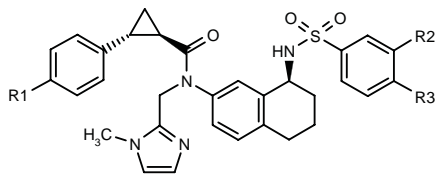
316559

(1*R*,2*R*)-2-(4-Fluorophenyl)-*N*-[8(*S*)-(3-fluorophenylsulfonamido)-5,6,7,8-tetrahydronaphthalen-2-yl]-*N*-(1-methyl-1*H*-imidazol-2-ylmethyl)cyclopropanecarboxamide



C31 H30 F2 N4 O3 S; Mol wt: 576.6650

ACTION – Voltage-dependent potassium Kv1.5 channel blocker found to produce 93% inhibition of potassium currents in CHO cells stably expressing the Kv1.5 potassium channel at 0.1 μM. Compound has a slow off-rate, as demonstrated by a peak current inhibition of 80%. Potentially useful for the treatment of cardiac arrhythmia. Other exemplified compounds are:



Compound	R1	R2	R3	Formula
316560	F	Cl	F	C ₃₁ H ₂₉ ClF ₂ N ₄ O ₃ S
316561	Cl	H	H	C ₃₁ H ₃₁ ClN ₄ O ₃ S
316562	Cl	H	Et	C ₃₃ H ₃₅ ClN ₄ O ₃ S

SOURCE – ICAgen.

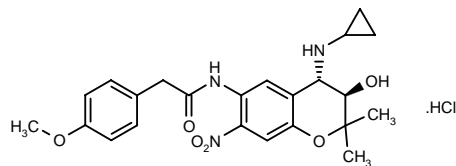
REFERENCES

1. Beaudoin, S. et al. (ICAgen, Inc.) *Potassium channel inhibitors*. WO 0208183.

NIP-141

281439

N-[(3*R**,4*S**)-4-(Cyclopropylamino)-3-hydroxy-2,2-dimethyl-7-nitro-3,4-dihydro-2*H*-1-benzopyran-6-yl]-2-(4-methoxyphenyl)acetamide hydrochloride



C23 H27 N3 O6 . HCl; Mol wt: 477.9422

ACTION – Antiarrhythmic agent proven to terminate atrial fibrillation in dogs by prolonging atrial refractoriness, without affecting conduction velocity. In human atrial myocytes, compound concentration-dependently blocked the transient outward current (*I*_{to}) and the ultrarapid delayed rectifier current (*I*_{Kur}) with respective IC₅₀ values of 16.3 and 5.3 μM; these currents were blocked in a voltage- and use-independent manner, and its effects were consistent with open channel block.

SOURCE – Nissan Chemical.

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1. Tanikawa, K. et al. (Nissan Chemical Industry, Ltd.) *Chroman derivs*. EP 0934296, JP 1998087650, US 6066631, WO 9804542.

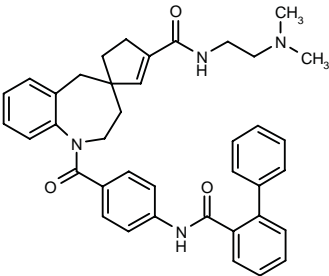
2. Seki, A. et al. *Effect of NIP-141 to human atrial muscle K channel*. Jpn J Electrocardiol 1999, 19(5): Abst 212.

3. Seki, A. et al. *Effects of NIP-141 on K currents in human atrial myocytes*. J Cardiovasc Pharmacol 2002, 39(1): 29.

HEART FAILURE THERAPY

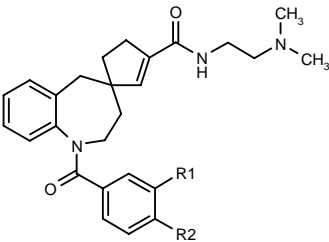
315383

1-[4-(Biphenyl-2-ylcarboxamido)benzoyl]-*N*-[2-(dimethyl-amino)ethyl]-1,2,3,5-tetrahydrospiro[1-benzazepine-4,1'-[2]cyclopentene]-3'-carboxamide isomer A



C39 H40 N4 O3; Mol wt: 612.7700

ACTION – Vasopressin receptor antagonist with IC₅₀ values of 0.003 and 0.016 μM, against vasopressin V_{1a} and V₂ receptors, respectively, while showing only 13% inhibition of V_{1b} receptor binding at 10 μM. In functional assays, compound displayed an IC₅₀ of 0.002 μM against V_{1a} receptors. Potentially useful for the treatment of congestive heart failure and cardiac insufficiency, as well as inner ear disorders, hypertension, coronary and renal vasospasm, cardiac ischemia, liver cirrhosis, renal failure, cerebral edema and ischemia, stroke, thrombosis, water retention, obsessive–compulsive disorders, dysmenorrhea, nephrotic syndrome and CNS injuries. Other exemplified spiro benzazepines include the following:



Compound	R1	R2	Isomer	Formula
315385	H	2-Ph-PhCONH	B	C ₃₉ H ₄₀ N ₄ O ₃
315386	H	2-F-PhCONH	A	C ₃₃ H ₃₅ FN ₄ O ₃
315387	H	2-F-PhCONH	B	C ₃₃ H ₃₅ FN ₄ O ₃
315388	OMe	2-(CH2OH)-1-pyrrolyl		C ₃₂ H ₃₈ N ₄ O ₄

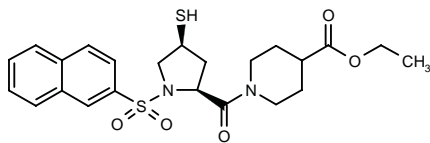
SOURCE – Ortho-McNeil.

REFERENCES

1. Chen, R.H. and Xiang, M.A. (Ortho-McNeil Pharmaceutical, Inc.) *Nonpeptide substid. spirobenzoazepines as vasopressin antagonists*. WO 0202531.

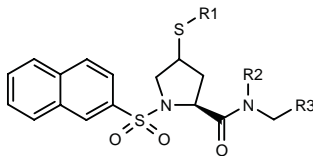
316212

1-[1-(Naphthalen-2-ylsulfonyl)-4(*S*)-sulfanyl-L-prolyl]-piperidine-4-carboxylic acid ethyl ester

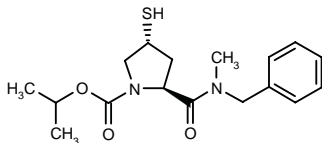


C23 H28 N2 O5 S2; Mol wt: 476.6152

ACTION – An inhibitor of metalloproteases, particularly zinc hydrolase, for use in the treatment of endothelin-converting enzyme (ECE)-mediated conditions including myocardial ischemia, congestive heart failure, arrhythmia, hypertension, pulmonary hypertension, asthma, cerebral vasospasm, subarachnoid hemorrhage, preeclampsia, kidney diseases, atherosclerosis, Burger’s disease, Takayasu’s arteritis, diabetic complications, lung and prostatic cancer, gastrointestinal disorders, endotoxic shock, wound healing, control of menstruation, glaucoma, transplant rejection, organ protection and diseases associated with cytostatic, ophthalmological and cerebro-protective indications. Other exemplified pyrrolidine derivatives include the following:



Compound	R1	R2	R3	Isomer	Formula
316217	H	Me	2-(CO2Me)-PhNHCO	R	C ₂₆ H ₂₇ N ₃ O ₆ S ₂
316221	H	Me	4-CO2H-PhN(Me)CH2CO	R	C ₂₆ H ₂₇ N ₃ O ₆ S ₂
316224	H	CH2Ph	CH2CO2H	R	C ₂₅ H ₂₆ N ₂ O ₅ S ₂
316226	H	i-BuCH2	CO2H	R	C ₂₂ H ₂₈ N ₂ O ₅ S ₂
316232	H	5-tetrazolyl-CH2CH2	Ph	R	C ₂₅ H ₂₆ N ₆ O ₃ S ₂
316233	H	Me	i-BuCO	R	C ₂₂ H ₂₈ N ₂ O ₄ S ₂
316234	Ac	-CH2CH2CH(CO2Et)CH2CH2-		S	C ₂₅ H ₃₀ N ₂ O ₆ S ₂



316229: C17 H24 N2 O3 S

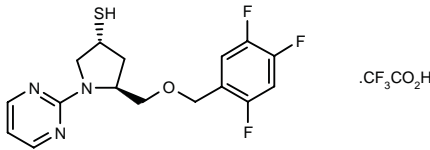
SOURCE – Roche.

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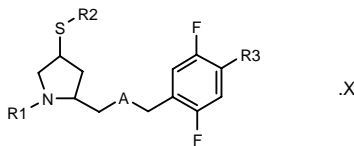
316235

1-(2-Pyrimidinyl)-5(*S*)-(2,4,5-trifluorobenzyloxymethyl)-pyrrolidine-3(*R*)-thiol trifluoroacetate



C16 H16 F3 N3 O S . C2 H F3 O2; Mol wt: 469.4043

ACTION – An inhibitor of metalloproteases, particularly zinc hydrolase, for use in the treatment of endothelin-converting enzyme (ECE)-mediated conditions including myocardial ischemia, congestive heart failure, arrhythmia, hypertension, pulmonary hypertension, asthma, cerebral vasospasm, subarachnoid hemorrhage, preeclampsia, kidney diseases, atherosclerosis, Burger’s disease, Takayasu’s arteritis, diabetic complications, lung and prostatic cancer, gastrointestinal disorders, endotoxic shock, wound healing, control of menstruation, glaucoma, transplant rejection, organ protection and diseases associated with cytostatic, ophthalmological and cerebroprotective indications. Other exemplified pyrrolidine derivatives include the following:



Compound	R1	R2	R3	A	Isomer	X	Formula
316238	6-Ph-3-pyridazinyl	H	F	O	3R,5S		C ₂₂ H ₂₀ F ₃ N ₃ OS
316239	5-Et-2-pyrimidinyl	H	F	O	3R,5S	CF3CO2H	C ₁₈ H ₂₀ F ₃ N ₃ OS .C ₂ HF ₃ O ₂
316240	5-CF3-2-Pyr	H	F	O	3R,5S	CF3CO2H	C ₁₇ H ₁₅ F ₆ N ₃ OS .C ₂ HF ₃ O ₂
316241	5-Pr-2-pyrimidinyl	Ac	F	O	3R,5S		C ₂₁ H ₂₄ F ₃ N ₃ O ₂ S
316242	5-(4-Pyr)-2-pyrimidinyl	H	F	O	3R,5S		C ₂₁ H ₁₉ F ₃ N ₄ OS
316244	5-(3-Pyr)-2-pyrimidinyl	H	F	O			C ₂₁ H ₁₉ F ₃ N ₄ OS
316245	5-Pr-2-pyrimidinyl	Ac	H	NH	3R,5S		C ₂₁ H ₂₆ F ₂ N ₄ OS

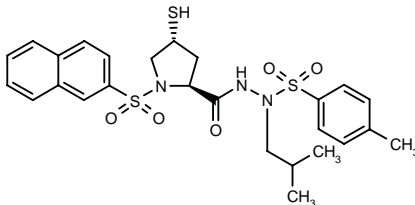
SOURCE – Roche.

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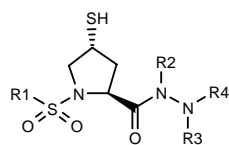
316248

1-(Naphthalen-2-ylsulfonyl)-4(*R*)-sulfanyl-L-proline *N'*-isobutyl-*N'*-(4-methylphenylsulfonyl)hydrazide



C26 H31 N3 O5 S3; Mol wt: 561.7449

ACTION – An inhibitor of metalloproteases, particularly zinc hydrolase, for use in the treatment of endothelin-converting enzyme (ECE)-mediated conditions including myocardial ischemia, congestive heart failure, arrhythmia, hypertension, pulmonary hypertension, asthma, cerebral vasospasm, subarachnoid hemorrhage, preeclampsia, kidney diseases, atherosclerosis, Burger’s disease, Takayasu’s arteritis, diabetic complications, lung and prostatic cancer, gastrointestinal disorders, endotoxic shock, wound healing, control of menstruation, glaucoma, transplant rejection, organ protection and diseases associated with cytostatic, ophthalmological and cerebro-protective indications. Other exemplified pyrrolidine derivatives include the following:



Compound	R1	R2	R3	R4	Formula
316252	2-Naph	H	H	Ph-CH2	C ₂₂ H ₂₃ N ₃ O ₃ S ₂
316253	2-Naph	H	Me	4-Me-Ph-SO2	C ₂₃ H ₂₅ N ₃ O ₅ S ₃
316254	2-Naph	H	H	1H-indol-3-yl-CH2CO	C ₂₅ H ₂₄ N ₄ O ₄ S ₂
316257	2-Naph	H	cyclopropyl-CH2	4-Me-Ph-SO2	C ₂₆ H ₂₉ N ₃ O ₅ S ₃
316258	2-Naph	H	2,5-(F)2-PhCH2	4-Me-Ph-SO2	C ₂₉ H ₂₇ F ₂ N ₃ O ₅ S ₃
316259	4-Ph-Ph	H	Me	4-Me-Ph-SO2	C ₂₆ H ₂₇ N ₃ O ₅ S ₃
316261	(F)5-Ph	H	H	4-Me-Ph-SO2	C ₁₈ H ₁₆ F ₅ N ₃ O ₅ S ₃
316262	2-Naph	Me	CH2Ph	4-Me-Ph-SO2	C ₃₀ H ₃₁ N ₃ O ₅ S ₃

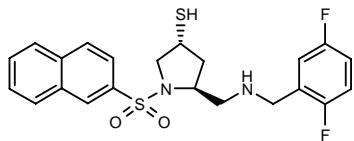
SOURCE – Roche.

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1. Aebi, J. et al. (F. Hoffmann-La Roche AG) *Pyrrolidine-2-carboxylic acid hydrazide derivs. for use as metalloprotease inhibitors*. WO 0206224.

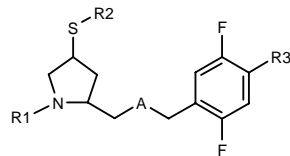
316678

5(S)-(2,5-Difluorobenzylaminomethyl)-1-(naphthalen-2-ylsulfonyl)pyrrolidine-3(R)-thiol



C22 H22 F2 N2 O2 S2; Mol wt: 448.5558

ACTION – An inhibitor of metalloproteases, particularly endothelin-converting enzyme (ECE). Potentially useful for the treatment of myocardial ischemia, congestive heart failure, arrhythmia, hypertension, pulmonary hypertension, asthma, cerebral vasospasm, subarachnoid hemorrhage, preeclampsia, kidney diseases, atherosclerosis, Burger’s disease, Takayasu’s arteritis, diabetic complications, lung and prostatic cancer, gastrointestinal disorders, endotoxic shock, wound healing, control of menstruation, glaucoma, transplant rejection, organ protection and diseases associated with cytostatic, ophthalmological and cerebroprotective indications. Other specifically claimed compounds are:



Compound	R1	R2	R3	A	Isomer	Formula
316679	4-F-PhOCO	H	H	N	2S,4R	C ₁₉ H ₁₉ F ₃ N ₂ O ₂ S
316680	2-Naph-OCO	H	H	N	2S,4R	C ₂₃ H ₂₂ F ₂ N ₂ O ₂ S
316681	CO2Bu	H	H	N	2S,4R	C ₁₇ H ₂₄ F ₂ N ₂ O ₂ S
316682	CO2Bu	H	F	O	2S,4R	C ₁₇ H ₂₂ F ₃ NO ₃ S
316683	SO2Me	H	F	O	3R,5S	C ₁₃ H ₁₆ F ₃ NO ₃ S ₂
316684	SO2NHCH2Ph	H	F	O	2S,4R	C ₁₉ H ₂₁ F ₃ N ₂ O ₃ S ₂
316685	4-F-PhCH2NHSO2	H	F	O		C ₁₉ H ₂₀ F ₄ N ₂ O ₃ S ₂
316686	2-(CO2Me)-PhOCO	Ac	F	O	2S,4R	C ₂₃ H ₂₂ F ₃ NO ₆ S

SOURCE – Roche.

REFERENCES

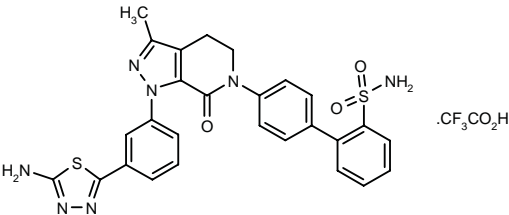
1. Aebi, J. et al. (F. Hoffmann-La Roche AG) *Pyrrolidine derivs. as metalloprotease inhibitors*. WO 0208185.

AGENTS AFFECTING BLOOD COAGULATION

ANTICOAGULANTS

315181

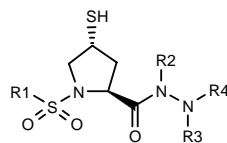
4'-[1-[3-(5-Amino-1,3,4-thiadiazol-2-yl)phenyl]-3-methyl-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridin-6-yl]biphenyl-2-sulfonamide trifluoroacetate



C27 H23 N7 O3 S2 . C2 H F3 O2; Mol wt: 671.6786

ACTION – Anticoagulant, a factor Xa inhibitor. Potentially useful for the treatment of thromboembolic disorders including unstable angina, myocardial infarction, ischemia, stroke, atherosclerosis, thrombosis, thrombophlebitis and arterial, cerebral, kidney and pulmonary embolism, among others. Other exemplified condensed pyrazole derivatives are:

ACTION – An inhibitor of metalloproteases, particularly zinc hydrolase, for use in the treatment of endothelin-converting enzyme (ECE)-mediated conditions including myocardial ischemia, congestive heart failure, arrhythmia, hypertension, pulmonary hypertension, asthma, cerebral vasospasm, subarachnoid hemorrhage, preeclampsia, kidney diseases, atherosclerosis, Burger’s disease, Takayasu’s arteritis, diabetic complications, lung and prostatic cancer, gastrointestinal disorders, endotoxic shock, wound healing, control of menstruation, glaucoma, transplant rejection, organ protection and diseases associated with cytostatic, ophthalmological and cerebro-protective indications. Other exemplified pyrrolidine derivatives include the following:



Compound	R1	R2	R3	R4	Formula
316252	2-Naph	H	H	Ph-CH2	C ₂₂ H ₂₃ N ₃ O ₃ S ₂
316253	2-Naph	H	Me	4-Me-Ph-SO2	C ₂₃ H ₂₅ N ₃ O ₅ S ₃
316254	2-Naph	H	H	1H-indol-3-yl-CH2CO	C ₂₅ H ₂₄ N ₄ O ₄ S ₂
316257	2-Naph	H	cyclopropyl-CH2	4-Me-Ph-SO2	C ₂₆ H ₂₉ N ₃ O ₅ S ₃
316258	2-Naph	H	2,5-(F)2-PhCH2	4-Me-Ph-SO2	C ₂₉ H ₂₇ F ₂ N ₃ O ₅ S ₃
316259	4-Ph-Ph	H	Me	4-Me-Ph-SO2	C ₂₆ H ₂₇ N ₃ O ₅ S ₃
316261	(F)5-Ph	H	H	4-Me-Ph-SO2	C ₁₈ H ₁₆ F ₅ N ₃ O ₅ S ₃
316262	2-Naph	Me	CH2Ph	4-Me-Ph-SO2	C ₃₀ H ₃₁ N ₃ O ₅ S ₃

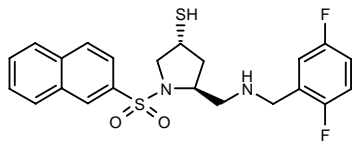
SOURCE – Roche.

REFERENCES

1. Aebi, J. et al. (F. Hoffmann-La Roche AG) *Pyrrolidine-2-carboxylic acid hydrazide derivs. for use as metalloprotease inhibitors*. WO 0206224.

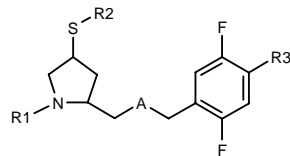
316678

5(S)-(2,5-Difluorobenzylaminomethyl)-1-(naphthalen-2-ylsulfonyl)pyrrolidine-3(R)-thiol



C22 H22 F2 N2 O2 S2; Mol wt: 448.5558

ACTION – An inhibitor of metalloproteases, particularly endothelin-converting enzyme (ECE). Potentially useful for the treatment of myocardial ischemia, congestive heart failure, arrhythmia, hypertension, pulmonary hypertension, asthma, cerebral vasospasm, subarachnoid hemorrhage, preeclampsia, kidney diseases, atherosclerosis, Burger’s disease, Takayasu’s arteritis, diabetic complications, lung and prostatic cancer, gastrointestinal disorders, endotoxic shock, wound healing, control of menstruation, glaucoma, transplant rejection, organ protection and diseases associated with cytostatic, ophthalmological and cerebroprotective indications. Other specifically claimed compounds are:



Compound	R1	R2	R3	A	Isomer	Formula
316679	4-F-PhOCO	H	H	N	2S,4R	C ₁₉ H ₁₉ F ₃ N ₂ O ₂ S
316680	2-Naph-OCO	H	H	N	2S,4R	C ₂₃ H ₂₂ F ₂ N ₂ O ₂ S
316681	CO2Bu	H	H	N	2S,4R	C ₁₇ H ₂₄ F ₂ N ₂ O ₂ S
316682	CO2Bu	H	F	O	2S,4R	C ₁₇ H ₂₂ F ₃ NO ₃ S
316683	SO2Me	H	F	O	3R,5S	C ₁₃ H ₁₆ F ₃ NO ₃ S ₂
316684	SO2NHCH2Ph	H	F	O	2S,4R	C ₁₉ H ₂₁ F ₃ N ₂ O ₃ S ₂
316685	4-F-PhCH2NHSO2	H	F	O		C ₁₉ H ₂₀ F ₄ N ₂ O ₃ S ₂
316686	2-(CO2Me)-PhOCO	Ac	F	O	2S,4R	C ₂₃ H ₂₂ F ₃ NO ₆ S

SOURCE – Roche.

REFERENCES

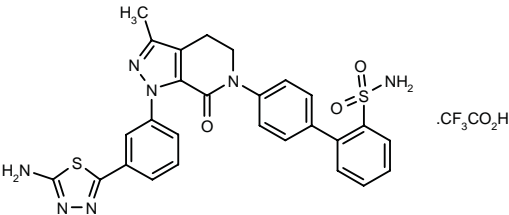
1. Aebi, J. et al. (F. Hoffmann-La Roche AG) *Pyrrolidine derivs. as metalloprotease inhibitors*. WO 0208185.

AGENTS AFFECTING BLOOD COAGULATION

ANTICOAGULANTS

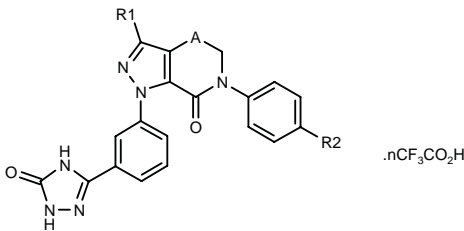
315181

4'-[1-[3-(5-Amino-1,3,4-thiadiazol-2-yl)phenyl]-3-methyl-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridin-6-yl]biphenyl-2-sulfonamide trifluoroacetate

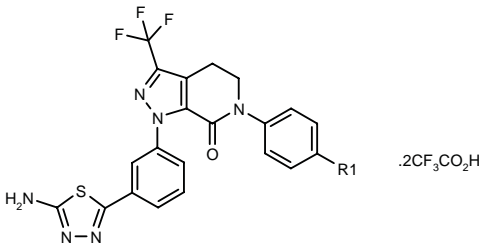


C27 H23 N7 O3 S2 . C2 H F3 O2; Mol wt: 671.6786

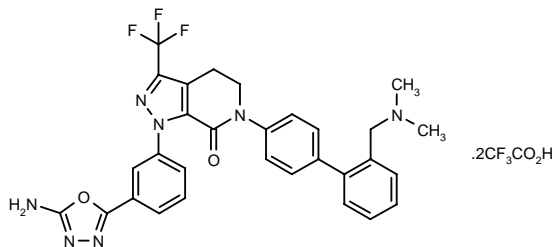
ACTION – Anticoagulant, a factor Xa inhibitor. Potentially useful for the treatment of thromboembolic disorders including unstable angina, myocardial infarction, ischemia, stroke, atherosclerosis, thrombosis, thrombophlebitis and arterial, cerebral, kidney and pulmonary embolism, among others. Other exemplified condensed pyrazole derivatives are:



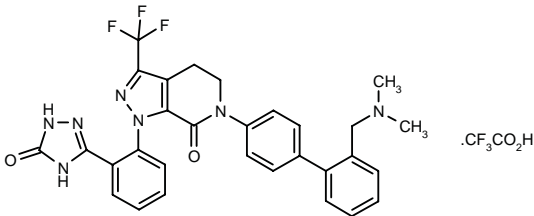
Compound	R1	R2	A	n	Formula
315182	CF3	2-(1-pyrrolidinyl-CH2)-Ph	-CH2-	1	C ₃₂ H ₂₆ F ₃ N ₇ O ₂ .C ₂ HF ₃ O ₂
315183	CF3	2-[3(S)-OH-1-pyrrolidinyl-CH2]-Ph	-CH2-	1	C ₃₂ H ₂₆ F ₃ N ₇ O ₃ .C ₂ HF ₃ O ₂
315185	CF3	2-[N(Me)2CH2]-Ph	-CH2-	2	C ₃₀ H ₂₆ F ₃ N ₇ O ₂ .2C ₂ HF ₃ O ₂
315186	CF3	2-(MeSO2)-Ph	-CH2-	0	C ₂₈ H ₂₁ F ₃ N ₆ O ₄ S
315192	CF3	2-[N(Me)2CH2]-1-imidazolyl	-CH2-	2	C ₂₇ H ₂₄ F ₃ N ₉ O ₂ .2C ₂ HF ₃ O ₂
315193	Me	2-(1-pyrrolidinyl-CH2)-1-imidazolyl	-CH2-	2	C ₂₉ H ₂₉ N ₉ O ₂ .2C ₂ HF ₃ O ₂
315194	CONH2	2-(1-pyrrolidinyl-CH2)-Ph	-CH2-	1	C ₃₂ H ₃₀ N ₈ O ₃ .C ₂ HF ₃ O ₂
315196	CF3	2-(1-pyrrolidinyl-CH2)-Ph	-(CH2)2-	1	C ₃₃ H ₃₀ F ₃ N ₇ O ₂ .C ₂ HF ₃ O ₂



Compound	R1	Formula
315188	2-[N(Me)2CH2]-Ph	C ₃₀ H ₂₆ F ₃ N ₇ OS.2C ₂ HF ₃ O ₂
315189	2-(1-pyrrolidinyl-CH2)-Ph	C ₃₂ H ₂₈ F ₃ N ₇ OS.2C ₂ HF ₃ O ₂
315190	2-[N(Me)2CH2]-1-imidazolyl	C ₂₇ H ₂₄ F ₃ N ₉ OS.2C ₂ HF ₃ O ₂
315191	2-(1-pyrrolidinyl-CH2)-1-imidazolyl	C ₂₉ H ₂₆ F ₃ N ₉ OS.2C ₂ HF ₃ O ₂



315187: C30 H26 F3 N7 O2 . 2 C2 H F3 O2



315197: C30 H26 F3 N7 O2 . C2 H F3 O2

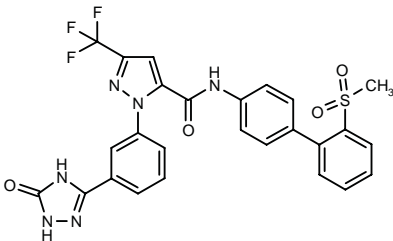
SOURCE – Bristol-Myers Squibb.

REFERENCES

1. Pinto, D.J.P. et al. (DuPont Pharmaceuticals Co.) 1-(Heteroaryl-phenyl)-condensed pyrazol derivs. as factor Xa inhibitors. WO 0200655.

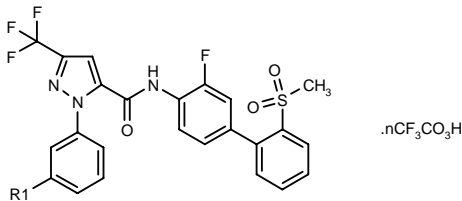
315255

N-[2'-(Methylsulfonyl)biphenyl-4-yl]-1-[3-(5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)phenyl]-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide

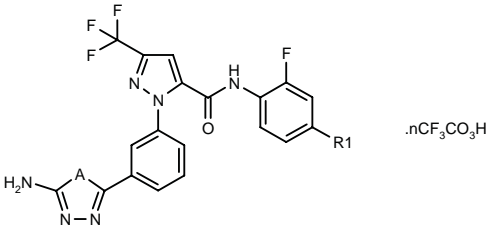


C26 H19 F3 N6 O4 S; Mol wt: 568.5341

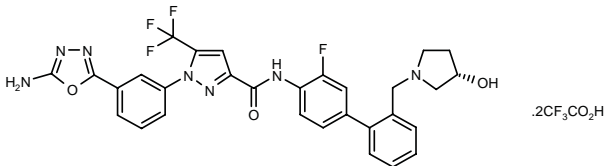
ACTION – Anticoagulant, a factor Xa inhibitor. Potentially useful for the treatment of thromboembolic disorders including unstable angina, myocardial infarction, ischemic sudden death, transient ischemic attack, stroke, atherosclerosis, venous thrombosis, deep venous thrombosis, thrombophlebitis, arterial embolism, coronary and cerebral arterial thrombosis, and cerebral, kidney and pulmonary embolism. Other exemplified heteroaryl-phenyl substituted compounds are:



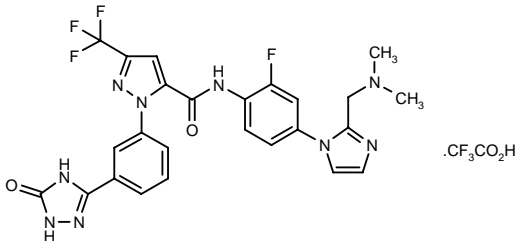
Compound	R1	n	Formula
315257	5-oxo-1-H-4,5-dihydro-1,2,4-triazol-3-yl	0	C ₂₆ H ₁₈ F ₄ N ₆ O ₄ S
315259	5-NH2-4H-1,2,4-triazol-3-yl	1	C ₂₆ H ₁₉ F ₄ N ₇ O ₃ S.C ₂ HF ₃ O ₂
315261	5-NH2-1,3,4-thiadiazol-2-yl	1	C ₂₆ H ₁₈ F ₄ N ₆ O ₃ S ₂ .C ₂ HF ₃ O ₂
315264	3-Pyr	1	C ₂₉ H ₂₀ F ₄ N ₄ O ₃ S.C ₂ HF ₃ O ₂
315267	4-Pyr	1	C ₂₉ H ₂₀ F ₄ N ₄ O ₃ S.C ₂ HF ₃ O ₂



Compound	R1	A	n	Formula
315263	2-Me-1-imidazolyl	S	1	C ₂₃ H ₁₆ F ₄ N ₆ OS.C ₂ HF ₃ O ₂
315269	2-[N(Me)2CH2]-Ph	O	2	C ₂₈ H ₂₃ F ₄ N ₇ O ₂ .2C ₂ HF ₃ O ₂
315270	2-[3(S)-OH-1-pyrrolidinyl-CH2]-Ph	O	2	C ₃₀ H ₂₅ F ₄ N ₇ O ₃ .2C ₂ HF ₃ O ₂



315272: C30 H25 F4 N7 O3 . 2 C2 H F3 O2



315262: C25 H21 F4 N9 O2 ·C2 H F3 O2

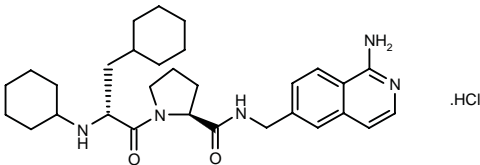
SOURCE – Bristol-Myers Squibb.

REFERENCES

1. Pinto, D.J.P. et al. (DuPont Pharmaceuticals Co.) *Heteroaryl-phenyl subst. factor Xa inhibitors*. WO 020647.

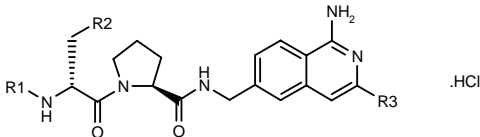
315557

N,3-Dicyclohexyl-D-alanyl-*N*¹-(1-aminoisoquinolin-6-ylmethyl)-L-prolinamide hydrochloride



C30 H43 N5 O2 . HCl; Mol wt: 542.1636

ACTION – Anticoagulant that acts via inhibition of thrombin (IC₅₀ = 0.03 μM). Potentially useful for the treatment of thrombin-related diseases such as deep venous thrombosis, pulmonary embolism, thrombophlebitis, arterial occlusion, restenosis following arterial injury, postoperative venous thrombosis or embolism, atherosclerosis, stroke, myocardial infarction, cancer and metastasis, and neurodegenerative diseases. Other exemplified 2-aminoisoquinoline-containing compounds are:



Compound	R1	R2	R3	Formula
315559	cyclohexyl	cyclohexyl	Me	C ₃₁ H ₄₈ N ₆ O ₂ ·HCl
315560	cyclohexyl	phenyl	H	C ₃₀ H ₃₇ N ₆ O ₂ ·HCl
315561	cyclopentyl	cyclohexyl	H	C ₂₉ H ₄₁ N ₆ O ₂ ·HCl
315562	i-Pr	cyclohexyl	H	C ₂₇ H ₃₈ N ₆ O ₂ ·HCl

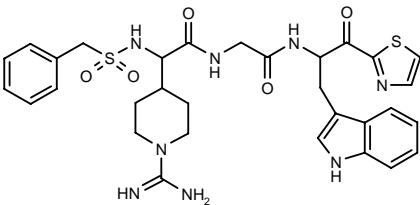
SOURCE – Akzo Nobel.

REFERENCES

1. Rewinkel, J.B.M. et al. (Akzo Nobel N.V.) *Thrombin inhibitors comprising an aminoisoquinoline group*. WO 0204423.

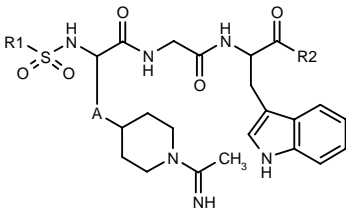
316081

2-[2-(1-Amidinopiperidin-4-yl)-*N*-(benzylsulfonyl)-DL-glycyl-glycyl-DL-tryptophyl]thiazole

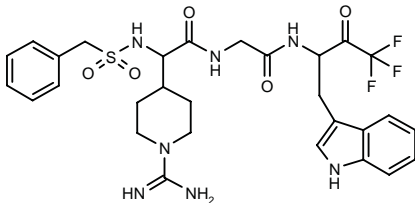


C31 H36 N8 O5 S2; Mol wt: 664.8084

ACTION – Anticoagulant, a factor Xa inhibitor with potential in the prevention and treatment of thrombosis associated with cardiovascular disorders such as unstable angina, refractory angina, myocardial infarction, transient ischemic attacks, thrombotic and embolic stroke, disseminated intravascular coagulation, septic shock, deep venous thrombosis, pulmonary embolism, reocclusion or restenosis of reperfused coronary arteries, peripheral arterial occlusion, occlusive coronary thrombus formation resulting from thrombolytic therapy or percutaneous transluminal coronary angioplasty, and thrombus formation in the venous vasculature. Other exemplified compounds are:



Compound	R1	R2	A	Formula
316082	CH2Ph	2-thiazolyl	bond	C ₃₂ H ₃₇ N ₇ O ₅ S ₂
316083	Me	2-thiazolyl	CH2	C ₂₇ H ₃₅ N ₇ O ₅ S ₂
316085	CH2Ph	CF3	bond	C ₃₀ H ₃₅ F ₃ N ₆ O ₅ S
316086	Me	CF3	CH2	C ₂₅ H ₃₃ F ₃ N ₆ O ₅ S



316084: C29 H34 F3 N7 O5 S

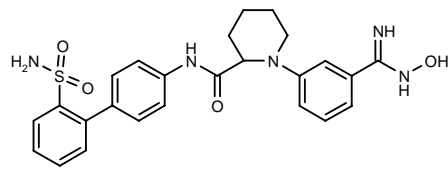
SOURCE – Millennium.

REFERENCES

1. Zhu, B.-Y. et al. (COR Therapeutics, Inc.) *Inhibitors of factor Xa*. WO 0206280.

316093

1-[3-(*N*-Hydroxyamidino)phenyl]-*N*-(2'-sulfamoylbiphenyl-4-yl)piperidine-2-carboxamide



C25 H27 N5 O4 S; Mol wt: 493.5853

ACTION – An inhibitor of factor Xa and factor VIIa with IC₅₀ values of 0.34 and 0.44 μM, respectively. Potentially useful for the treatment of thrombosis, myocardial infarction, arteriosclerosis, inflammation, stroke, angina pectoris, postangioplasty restenosis, intermittent claudication and cancer.

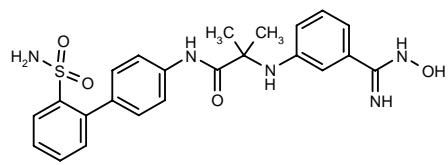
SOURCE – Merck KGaA.

REFERENCES

1. Juraszyk, H. et al. (Merck Patent GmbH) *Cyclic amino acid derivs.* DE 10035144, WO 0206269.

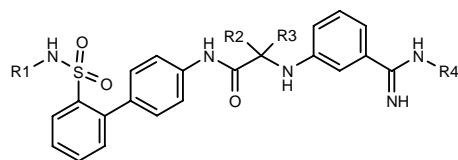
316663

2-[3-(*N*-Hydroxyamidino)phenylamino]-2-methyl-*N*-(2'-sulfamoylbiphenyl-4-yl)propionamide



C23 H25 N5 O4 S; Mol wt: 467.5475

ACTION – Agent with the ability to inhibit factor Xa and factor VIIa, potentially useful for the treatment of thrombosis, myocardial infarction, arteriosclerosis, inflammation, stroke, angina pectoris, postangioplasty restenosis, intermittent claudication and cancer. Other specifically claimed 1-amino-1,1-dialkylcarboxylic acid derivatives are:



Compound	R1	R2	R3	R4	Formula
316664	t-Bu	Me	Me	H	C ₂₇ H ₃₃ N ₅ O ₃ S
316665	H	-(CH ₂) ₄ -		OH	C ₂₅ H ₂₇ N ₅ O ₃ S
316667	t-Bu	-(CH ₂) ₄ -		H	C ₂₉ H ₃₅ N ₅ O ₃ S
316669	H	Me	Me	H	C ₂₃ H ₂₅ N ₅ O ₃ S
316671	H	-(CH ₂) ₄ -		H	C ₂₅ H ₂₇ N ₅ O ₃ S
316673	H	-(CH ₂) ₅ -		H	C ₂₆ H ₂₉ N ₅ O ₃ S

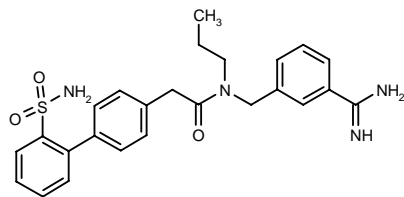
SOURCE – Merck KGaA.

REFERENCES

1. Juraszyk, H. et al. (Merck Patent GmbH) *N-Substd.-1-amino-1,1-dialkylcarboxylic acid derivs.* DE 10036121, WO 0208177.

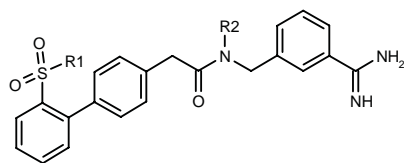
316856

N-(3-Amidinobenzyl)-*N*-propyl-2-(2'-sulfamoylbiphenyl-4-yl)acetamide



C25 H28 N4 O3 S; Mol wt: 464.5872

ACTION – Anticoagulant, a factor Xa and/or factor VIIa inhibitor, potentially useful for the treatment of thrombosis, myocardial infarction, arteriosclerosis, inflammation, stroke, angina pectoris, postangioplasty restenosis, intermittent claudication and cancer. Other specifically claimed acetamide derivatives are:



Compound	R1	R2	Formula
316857	Me	Pr	C ₂₆ H ₂₉ N ₃ O ₃ S
316858	NH2	Ph	C ₂₈ H ₂₆ N ₄ O ₃ S

SOURCE – Merck KGaA.

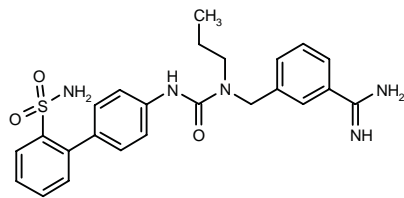
REFERENCES

1. Mederski, W. et al. (Merck Patent GmbH) *Acetamide derivs. and the use thereof as inhibitors of coagulation factor Xa and VIIa.* DE 10037146, WO 0210127.

316862

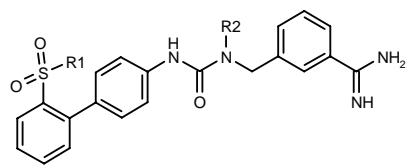
3-[1-Propyl-3-(2'-sulfamoylbiphenyl-4-yl)ureidomethyl]-benzamide

N-(3-Amidinobenzyl)-*N*-propyl-*N'*-(2'-sulfamoylbiphenyl-4-yl)urea



C24 H27 N5 O3 S; Mol wt: 465.5753

ACTION – Anticoagulant, a factor Xa and/or factor VIIa inhibitor, potentially useful for the treatment of thrombosis, myocardial infarction, arteriosclerosis, inflammation, stroke, angina pectoris, postangioplasty restenosis, intermittent claudication and cancer. Other specifically claimed urea derivatives are:



Compound	R1	R2	Formula
316864	Me	Pr	C ₂₅ H ₂₈ N ₄ O ₃ S
316865	NH2	Ph	C ₂₇ H ₂₅ N ₅ O ₃ S
316866	Me	Ph	C ₂₈ H ₂₆ N ₄ O ₃ S

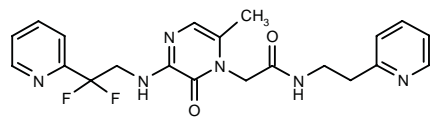
SOURCE – Merck KGaA.

REFERENCES

1. Mederski, W. et al. (Merck Patent GmbH) *Urethane derivs.* DE 10036852, WO 0210145.

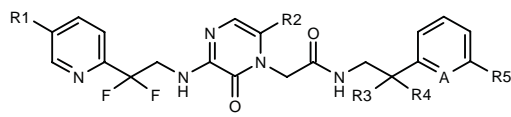
316878

2-[3-[2,2-Difluoro-2-(2-pyridyl)ethylamino]-6-methyl-2-oxo-1,2-dihydropyrazin-1-yl]-N-[2-(2-pyridyl)ethyl]-acetamide



C21 H22 F2 N6 O2; Mol wt: 428.4408

ACTION – Antithrombotic agent with a K_i value of < 20 nM for thrombin. Potentially useful for the treatment of venous thromboembolism, deep vein thrombosis, thromboembolic stroke, atherosclerosis, reocclusion associated with percutaneous transluminal coronary angioplasty and occlusive cerebrovascular disease, as well as for maintaining vascular patency in a patient. Other exemplified 1,2-dihydropyrazin-2-one derivatives are:



Compound	R1	R2	R3	R4	R5	A	Formula
316879	H	Me	F	F	H	N	C ₂₁ H ₂₀ F ₄ N ₆ O ₂
316880	H	Me	H	H	Cl	CH	C ₂₂ H ₂₂ ClF ₂ N ₅ O ₂
316881	H	Me	H	H	H	CH	C ₂₂ H ₂₃ F ₂ N ₅ O ₂
316882	H	Cl	F	F	H	N	C ₂₀ H ₁₇ ClF ₄ N ₆ O ₂
316883	Me	Me	F	F	H	N	C ₂₂ H ₂₂ F ₄ N ₆ O ₂

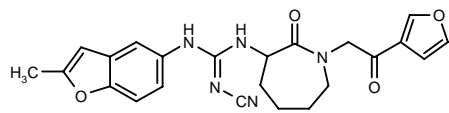
SOURCE – Merck & Co.

REFERENCES

1. Isaacs, R.C. et al. (Merck & Co., Inc.) *Thrombin inhibitors.* WO 0209711.

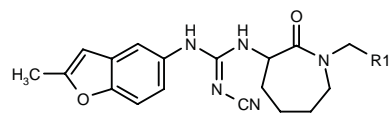
316923

N²-Cyano-N¹-[1-[2-(3-furyl)acetyl]-2-oxoperhydroazepin-3-yl]-N³-(2-methyl-1-benzofuran-5-yl)guanidine

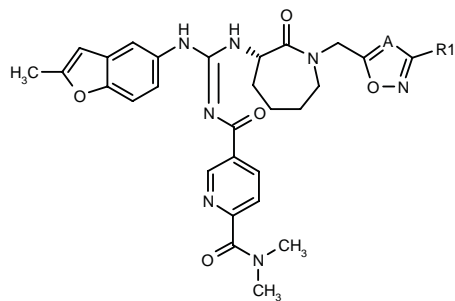


C23 H23 N5 O4; Mol wt: 433.4657

ACTION – An inhibitor of factor Xa, potentially useful for the treatment of myocardial infarction, unstable angina, thromboembolic stroke, venous thrombosis, pulmonary embolism, peripheral occlusive consequences of surgery, interventional cardiology or immobility, thrombotic consequences of atherosclerosis, disseminated intravascular coagulation, and thromboembolic effects of thrombophilia. Other specifically claimed compounds are:



Compound	R1	Formula
316924	CH2Ph	C ₂₅ H ₂₇ N ₅ O ₂
316925	3-CO2H-Ph	C ₂₅ H ₂₅ N ₅ O ₄
316926	3-[N(Me)2CO]-Ph	C ₂₇ H ₃₀ N ₆ O ₃



Compound	R1	A	Formula
316928	N(Me)2	N	C ₃₀ H ₃₅ N ₉ O ₅
316929	Ph	N	C ₃₄ H ₃₄ N ₈ O ₅
316930	4-CF3-3-Pyr	N	C ₃₄ H ₃₂ F ₃ N ₉ O ₅
316931	2-Cl-PhOCH2	N	C ₃₅ H ₃₅ ClN ₈ O ₆
316932	Ph	CH	C ₃₅ H ₃₅ N ₇ O ₅

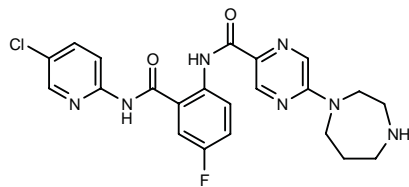
SOURCE – Bristol-Myers Squibb.

REFERENCES

1. Stein, P.D. et al. (Bristol-Myers Squibb Co.) *Lactam inhibitors of factor Xa which are useful for the treatment of thrombosis.* WO 0210159.

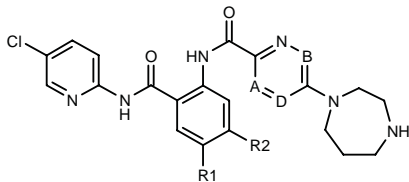
316936

N-[2-[*N*-(5-Chloropyridin-2-yl)carbamoyl]-4-fluorophenyl]-5-(perhydro-1,4-diazepin-1-yl)pyrazine-2-carboxamide



C22 H21 Cl F N7 O2; Mol wt: 469.9059

ACTION – Anticoagulant, a factor Xa inhibitor, potentially useful for the treatment of thromboembolic disorders including venous thrombosis, pulmonary embolism, arterial thrombosis, myocardial infarction, unstable angina, stroke, atherosclerosis, and general and local hypercoagulable states. Other specifically claimed substituted heterocyclic amides are:



Compound	R1	R2	A	B	D	Formula
316937	F	H	CH	N	CH	C ₂₂ H ₂₁ ClFN ₇ O ₂
316938	F	H	N	CH	CH	C ₂₂ H ₂₁ ClFN ₇ O ₂
316939	F	H	CH	CH	CH	C ₂₃ H ₂₂ ClFN ₆ O ₂
316940	H	CO ₂ Me	CH	CH	N	C ₂₅ H ₂₅ ClN ₆ O ₄

SOURCE – Lilly.

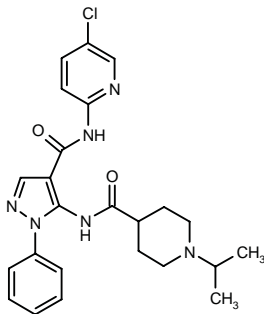
REFERENCES

1. Herron, D.K. et al. (Eli Lilly and Company) *Substd. heterocyclic amides*. WO 0210154.

AG-2418-00

315250

N-[4-[*N*-(5-Chloropyridin-2-yl)carbamoyl]-1-phenyl-1*H*-pyrazol-5-yl]-1-isopropylpiperidine-4-carboxamide



C24 H27 Cl N6 O2; Mol wt: 466.9703

ACTION – Anticoagulant, a factor Xa inhibitor, potentially useful for the treatment of thromboembolic disorders including unstable angina, myocardial infarction, ischemic sudden death, transient ischemic attack, stroke, atherosclerosis, venous thrombosis, deep venous thrombosis, thrombophlebitis, arterial embolism, coronary and cerebral arterial thrombosis, and cerebral, kidney and pulmonary embolism.

SOURCE – Bristol-Myers Squibb.

REFERENCES

1. Quan, M.L. et al. (DuPont Pharmaceuticals Co.) *Factor Xa inhibitors*. WO 0200651.

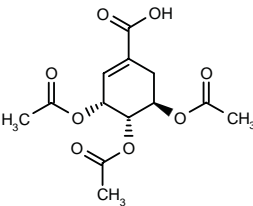
ANTIPLATELET THERAPY

TRIACETYLSHIKIMIC ACID

315306

3(*R*),4(*S*),5(*R*)-Triacetoxy-1-cyclohexene-1-carboxylic acid

TSA



C13 H16 O8; Mol wt: 300.2614

ACTION – Antiplatelet and antithrombotic agent, a shikimic acid derivative able to dose-dependently inhibit *ex vivo* platelet aggregation induced by ADP, collagen or arachidonic acid in rats, producing 82.9, 56.1 and 53.9% inhibition, respectively, at 200 mg/kg/day p.o. for 3 days; this effect was comparable to that of aspirin. In an arteriovenous shunt model of thrombosis in rats, compound dose-dependently reduced thrombus weight, with a maximum effect of 74.6% at 200 mg/kg p.o. No effect was seen on prothrombin time, activated partial thromboplastin time or thrombin time at effective antiplatelet doses, indicating that the coagulation system was not affected. Triacetylshikimic acid was also found to inhibit platelet–neutrophil adhesion induced by thrombin *in vitro* or by reperfusion injury in a model of focal cerebral ischemia in rats.

SOURCES – Beijing University of Chinese Medicine, Beijing (CN); CINVESTAN-I.P.N., Mexico D.F. (MX).

REFERENCES

1. Guo, Y. et al. (Beijing University of Chinese Medicine) *Pharmaceutical compsns. containing shikimic acid and its derivs., and its use in preparing anti-thrombosis and analgesic agents*. CN 1163104.

2. Chong, Z.Z. et al. *Effects and mechanisms of triacetylshikimic acid on platelet adhesion to neutrophils induced by thrombin and reperfusion after focal cerebral ischemia in rats*. Acta Pharmacol Sin 2001, 22(8): 679.

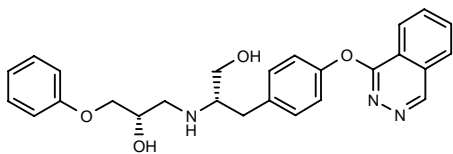
3. Huang, F. et al. *Anti-platelet and anti-thrombotic effects of triacetylshikimic acid in rats*. J Cardiovasc Pharmacol 2002, 39(2): 262.

RENAL-UROLOGIC DRUGS

TREATMENT OF URINARY INCONTINENCE

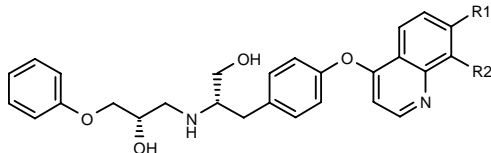
315202

2(S)-[2(S)-Hydroxy-3-phenoxypropylamino]-3-[4-(phthalazin-1-yloxy)phenyl]propan-1-ol



C26 H27 N3 O4; Mol wt: 445.5163

ACTION – Selective β_3 -adrenoceptor agonist found to inhibit the carbachol-induced increase in intravesical pressure by 35.9% following intraduodenal administration to anesthetized dogs at 0.32 mg/kg. Potentially useful for the treatment of urinary incontinence and pollakiuria. Other specifically claimed aminoalcohol derivatives are:



Compound	R1	R2	Formula
315206	CONHSO2Pr	H	C ₃₁ H ₃₅ N ₃ O ₇ S
315207	CONHCH2CH2CO2H	H	C ₃₁ H ₃₃ N ₃ O ₇
315208	H	CONHCH2CH2OH	C ₃₀ H ₃₃ N ₃ O ₆

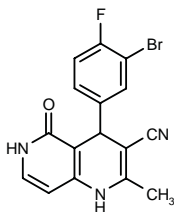
SOURCE – Fujisawa.

REFERENCES

1. Kayakiri, H. et al. (Fujisawa Pharmaceutical Co., Ltd.) *New aminoalcohol derivs.* WO 0200622.

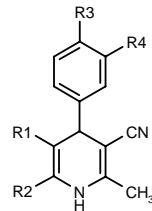
316829

4-(3-Bromo-4-fluorophenyl)-2-methyl-5-oxo-1,4,5,6-tetrahydro-1,6-naphthyridine-3-carbonitrile



C16 H11 Br F N3 O; Mol wt: 360.1849

ACTION – Potassium channel opener giving an EC₅₀ of 0.017 μ M against potassium channels in guinea pig urinary bladder smooth muscle cells. In a functional assay using isolated pig bladder strips, compound was shown to reduce stimulated contractions with 98% efficacy relative to P-1075 and a pD₂ of 6.85. Potentially useful for the treatment of bladder overactivity, benign prostatic hyperplasia, dysmenorrhea, preterm labor, urinary incontinence, male erectile dysfunction, premature ejaculation and female sexual dysfunction. Other exemplified bicyclic dihydropyridine compounds are:



Compound	R1,R2	R3	R4	Isomer	Formula
316830	-CONHCH2CH2-	Cl	NO2		C ₁₆ H ₁₃ ClN ₄ O ₃
316831	-C(Cl)=NCH=CH-	F	Br	racemic	C ₁₆ H ₁₀ BrClFN ₃
316832	-C(Cl)=NCH=CH-	F	Br	isomer A	C ₁₆ H ₁₀ BrClFN ₃
316833	-CON(Me)CH=CH-	F	Br		C ₁₇ H ₁₃ BrFN ₃ O

SOURCE – Abbott.

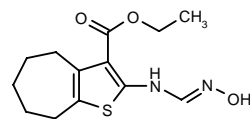
REFERENCES

1. Agrios, K. (Abbott Laboratories Inc.) *Dihydronaphthyridine potassium channel openers.* WO 0210164.

TREATMENT OF RENAL DISEASES

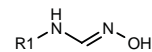
315195

2-(Hydroxyiminomethylamino)-5,6,7,8-tetrahydro-4H-cyclohepta[b]thiophene-3-carboxylic acid ethyl ester



C13 H18 N2 O3 S; Mol wt: 282.3622

ACTION – Agent with the ability to inhibit the production of 20-HETE, as demonstrated in rat kidney microsomes (81.4% inhibition at 1 μ M). Potentially useful for the treatment of nephropathy, cerebrovascular diseases and circulatory organ diseases. Other exemplified *N*-hydroxy-formamidine derivatives are:



Compound	R1	Formula
315198	3-(CO2Et)-4,5,6,7-tetrahydro-1-benzothien-2-yl	C ₁₂ H ₁₆ N ₂ O ₃ S
315199	2-CONH2-5-t-Bu-3-thienyl	C ₁₀ H ₁₅ N ₃ O ₂ S
315200	1-(PhCH2)-2-benzimidazolyl	C ₁₅ H ₁₄ N ₄ O

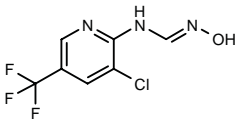
SOURCE – Taisho.

REFERENCES

1. Sato, M. et al. (Taisho Pharmaceutical Co., Ltd.) *Hydroxyformamidine cpds. and their salts, and medicines containing them*. JP 2001354658.

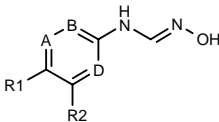
315201

*N*¹-[3-Chloro-5-(trifluoromethyl)pyridin-2-yl]-*N*²-hydroxyformamidine

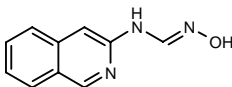


C7 H5 Cl F3 N3 O; Mol wt: 239.5835

ACTION – Agent with the ability to inhibit the production of 20-HETE, as demonstrated in rat kidney microsomes (108.1% inhibition at 1 μM). Potentially useful for the treatment of nephropathy, cerebrovascular diseases and circulatory organ diseases. Other exemplified *N*-hydroxyformamidine derivatives are:



Compound	R1	R2	A	B	D	Formula
315203	H	Me	CH	N	CH	C ₇ H ₉ N ₃ O
315204	I	H	CH	N	N	C ₆ H ₅ IN ₄ O
315205	CF ₃	H	CH	N	CH	C ₇ H ₆ F ₃ N ₃ O
315209	H	H	N	C(2-F-PhO)	CH	C ₁₂ H ₁₀ FN ₃ O ₂
315211	H	Pr	CH	CH	N	C ₉ H ₁₃ N ₃ O
315212	H	Et	CH	CH	N	C ₈ H ₁₁ N ₃ O



315210: C10 H9 N3 O

SOURCE – Taisho.

REFERENCES

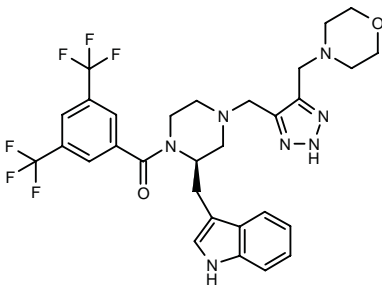
1. Sato, M. et al. (Taisho Pharmaceutical Co., Ltd.) *Hydroxyformamidine cpds. and their salts, and medicines containing them*. JP 2001354656.

GASTROINTESTINAL DRUGS

AGENTS FOR IRRITABLE BOWEL SYNDROME

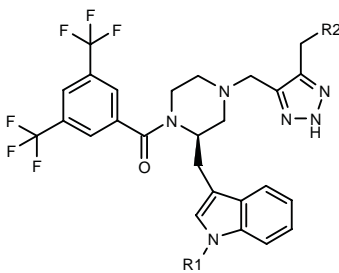
316266

1-[3,5-Bis(trifluoromethyl)phenyl]-1-[2(*R*)-(1*H*-indol-3-ylmethyl)-4-[5-(morpholin-4-ylmethyl)-2*H*-1,2,3-triazol-4-ylmethyl]piperazin-1-yl]methanone



C30 H31 F6 N7 O2; Mol wt: 635.6099

ACTION – A selective antagonist of tachykinin NK₁ receptors that demonstrated functional antagonism against pig aortic NK₁ receptors (pEC₅₀ = 9.0). *In vivo*, it was shown to inhibit substance P-induced hypotension in pigs following either i.v. or p.o. administration (pED₅₀ = 7.6 and 6.2, respectively). In addition, compound was devoid of calcium-antagonist effect, since it induced no decrease in blood pressure at all doses tested (up to 0.1 μmol/kg i.v., up to 3.2 μmol/kg p.o.). Potentially useful for the treatment of irritable bowel syndrome and other gastrointestinal disorders. Other exemplified *N*-triazolylmethyl-piperazine derivatives are:



Compound	R1	R2	Formula
316267	H	1-Piz	C ₃₀ H ₃₂ F ₆ N ₈ O
316268	Me	4-morpholinyl	C ₃₁ H ₃₃ F ₆ N ₇ O ₂
316269	H	N(Me)2	C ₂₈ H ₂₉ F ₆ N ₇ O
316271	H	N(Et)2	C ₃₀ H ₃₃ F ₆ N ₇ O
316274	H	N(i-Pr)2	C ₃₂ H ₃₇ F ₆ N ₇ O

SOURCE – Solvay.

REFERENCES

1. Jasserand, D. et al. (Solvay Pharmaceuticals GmbH) *N-Triazolylmethyl-piperazine derivs. as neurokinine receptor-antagonists*. DE 10036818, EP 1176144.

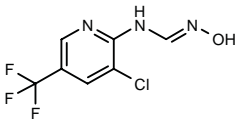
SOURCE – Taisho.

REFERENCES

1. Sato, M. et al. (Taisho Pharmaceutical Co., Ltd.) *Hydroxyformamidine cpds. and their salts, and medicines containing them*. JP 2001354658.

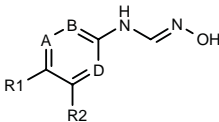
315201

N¹-[3-Chloro-5-(trifluoromethyl)pyridin-2-yl]-N²-hydroxyformamidine

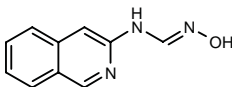


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315203	H	Me	CH	N	CH	C ₇ H ₉ N ₃ O
315204	I	H	CH	N	N	C ₅ H ₅ IN ₄ O
315205	CF ₃	H	CH	N	CH	C ₇ H ₆ F ₃ N ₃ O
315209	H	H	N	C(2-F-PhO)	CH	C ₁₂ H ₁₀ FN ₃ O ₂
315211	H	Pr	CH	CH	N	C ₉ H ₁₃ N ₃ O
315212	H	Et	CH	CH	N	C ₈ H ₁₁ N ₃ O



315210: C10 H9 N3 O

SOURCE – Taisho.

REFERENCES

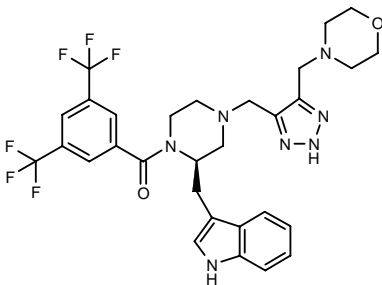
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GASTROINTESTINAL DRUGS

AGENTS FOR IRRITABLE BOWEL SYNDROME

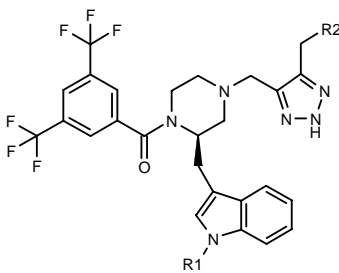
316266

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316269	H	N(Me)2	C ₂₈ H ₂₉ F ₆ N ₇ O
316271	H	N(Et)2	C ₃₀ H ₃₃ F ₆ N ₇ O
316274	H	N(<i>i</i> -Pr)2	C ₃₂ H ₃₇ F ₆ N ₇ O

SOURCE – Solvay.

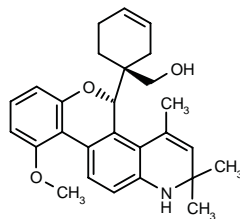
REFERENCES

1. Jasserand, D. et al. (Solvay Pharmaceuticals GmbH) *N-Triazolylmethyl-piperazine derivs. as neurokinine receptor-antagonists*. DE 10036818, EP 1176144.

INFLAMMATORY BOWEL DISEASE
THERAPY

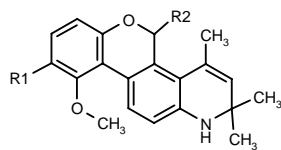
315369

(-)-1-[1(*R*)-[10-Methoxy-2,2,4-trimethyl-2,5-dihydro-1*H*-1-benzopyran[3,4-*h*]quinolin-5(*S*)-yl]-3-cyclohexen-1-yl]methanol



C27 H31 N O3; Mol wt: 417.5459

ACTION – A selective glucocorticoid receptor modulator shown to inhibit the binding of [³H]-dexamethasone to human glucocorticoid receptors and [³H]-progesterone to human progesterone A receptors with K_i values of 0.86 and 10,000 nM, respectively. Potentially useful for the treatment of inflammatory, immune and autoimmune diseases including inflammatory bowel disease, systemic lupus erythematosus, arthritis, hay fever, allergic rhinitis, urticaria, angioneurotic edema, chronic obstructive pulmonary disease, asthma, Crohn’s disease, ulcerative colitis, hepatitis, transplant rejection, cirrhosis, etc. Other exemplified compounds include the following:



Compound	R1	R2	Isomer	Formula
315370	OH	CH2C(=CH2)CH2OH		C ₂₄ H ₂₇ NO ₄
315371	H	3-(CH2CH2OH)-Ph		C ₂₈ H ₂₉ NO ₃
315374	OH	3-(CH2OH)-2-cyclohexenyl	R*,R*	C ₂₇ H ₃₁ NO ₄

SOURCES – Abbott; Ligand.

REFERENCES

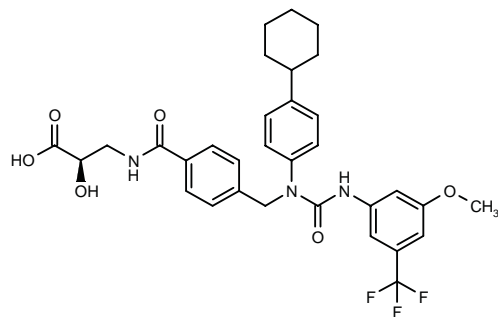
1. Coghlan, M.J. et al. (Ligand Pharmaceuticals, Inc.;Abbott Laboratories Inc.) *Glucocorticoid-selective antiinflammatory agents*. WO 0202565.

ENDOCRINE DRUGS

ANTIDIABETIC DRUGS

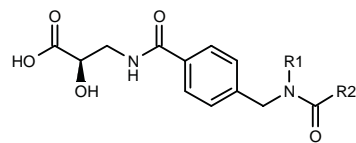
315282

3-[4-[1-(4-Cyclohexylphenyl)-3-[3-methoxy-5-(trifluoromethyl)phenyl]ureidomethyl]benzamido]-2(*R*)-hydroxypropionic acid



C32 H34 F3 N3 O6; Mol wt: 613.6296

ACTION – Glucagon antagonist or inverse agonist, potentially useful for the treatment of hyperglycemia, impaired glucose tolerance, type 1 and type 2 diabetes, obesity and dyslipidemia. Other exemplified amido-substituted carboxylic acid derivatives are:



Compound	R1	R2	Formula
315284	4-(1-cyclohexenyl)-Ph	3-CF3-5-MeO-PhNH	C ₃₂ H ₃₂ F ₃ N ₃ O ₆
315286	4-(1-cyclohexenyl)-Ph	3-Cl-PhNH	C ₃₀ H ₃₀ ClN ₃ O ₅
315287	4-(1-cyclohexenyl)-Ph	2,2,4,4-(F)4-2H,4H-1,3-benzodioxin-6-yl-NH	C ₃₂ H ₂₉ F ₄ N ₃ O ₇
315289	4-t-Bu-Ph	3,4-(Cl)2-PhNH	C ₂₈ H ₂₉ Cl ₂ N ₃ O ₅
315291	4-cyclohexyl-Ph	4-F-3-NO2-PhNH	C ₃₁ H ₃₄ FN ₃ O ₅
315296	CH2CH(Ph)2	4-(CF3O)-PhCH2	C ₃₄ H ₃₁ F ₃ N ₂ O ₆
315297	4-cyclohexyl-Ph	4-Ph-PhCH2	C ₃₇ H ₃₈ N ₂ O ₅
315298	4-cyclohexyl-Ph	3-NO2-PhCH2CH2	C ₃₃ H ₃₈ N ₂ O ₅

SOURCE – Novo Nordisk.

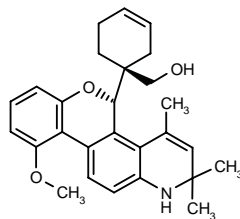
REFERENCES

1. Joergensen, A.S. et al. (Novo Nordisk A/S) *Glucagon antagonists/inverse agonists*. WO 0200612.

INFLAMMATORY BOWEL DISEASE
THERAPY

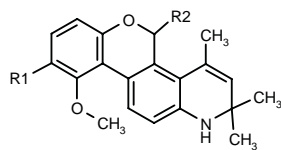
315369

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Compound	R1	R2	Isomer	Formula
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315371	H	3-(CH2CH2OH)-Ph		C ₂₈ H ₂₉ NO ₃
315374	OH	3-(CH2OH)-2-cyclohexenyl	R*,R*	C ₂₇ H ₃₁ NO ₄

SOURCES – Abbott; Ligand.

REFERENCES

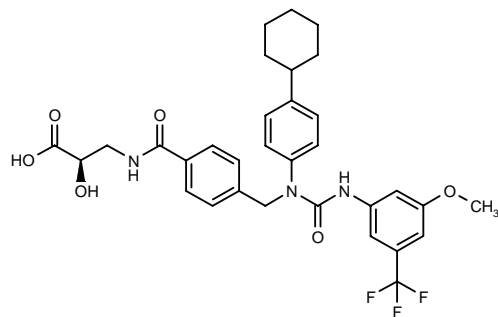
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ENDOCRINE DRUGS

ANTIDIABETIC DRUGS

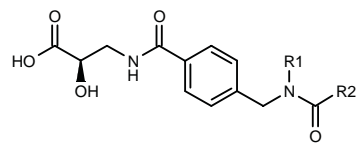
315282

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315286	4-(1-cyclohexenyl)-Ph	3-Cl-PhNH	C ₃₀ H ₃₀ ClN ₃ O ₅
315287	4-(1-cyclohexenyl)-Ph	2,2,4,4-(F)4-2H,4H-1,3-benzodioxin-6-yl-NH	C ₃₂ H ₂₈ F ₄ N ₃ O ₇
315289	4-t-Bu-Ph	3,4-(Cl)2-PhNH	C ₂₈ H ₂₆ Cl ₂ N ₃ O ₅
315291	4-cyclohexyl-Ph	4-F-3-NO2-PhNH	C ₃₁ H ₃₄ FN ₃ O ₅
315296	CH2CH(Ph)2	4-(CF3O)-PhCH2	C ₃₄ H ₃₁ F ₃ N ₂ O ₆
315297	4-cyclohexyl-Ph	4-Ph-PhCH2	C ₃₇ H ₃₈ N ₂ O ₅
315298	4-cyclohexyl-Ph	3-NO2-PhCH2CH2	C ₃₃ H ₃₈ N ₂ O ₅

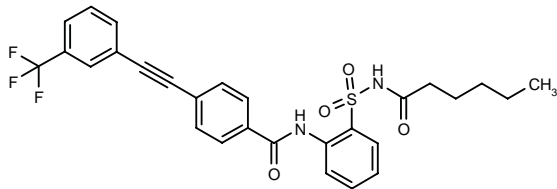
SOURCE – Novo Nordisk.

REFERENCES

1. Joergensen, A.S. et al. (Novo Nordisk A/S) *Glucagon antagonists/inverse agonists*. WO 0200612.

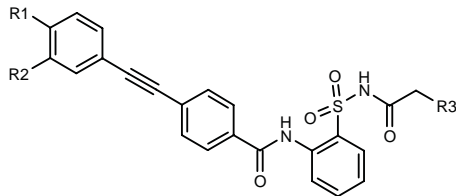
315785

N-[2-(Hexanamidosulfonyl)phenyl]-4-[3-(trifluoromethyl)-phenylethynyl]benzamide



C28 H25 F3 N2 O4 S; Mol wt: 542.5755

ACTION – Hypoglycemic agent found to increase glucose uptake by rat skeletal muscle cells by 246% (compared to controls) at 10 μM. In a mouse model of non-insulin-dependent diabetes mellitus, compound induced a 51.1% decrease in blood glucose levels when administered at 30 mg/kg twice daily for 1 week. It is reportedly devoid of side effects associated with glitazone analogues. Other exemplified acylsulfonamide derivatives are:



Compound	R1	R2	R3	Formula
315786	H	CF3	CH2CH2Ac	C ₂₈ H ₂₃ F ₃ N ₂ O ₅ S
315787	H	CF3	OPr	C ₂₇ H ₂₃ F ₃ N ₂ O ₅ S
315788	CF3	H	Bu	C ₂₈ H ₂₅ F ₃ N ₂ O ₄ S
315789	OCF3	H	Bu	C ₂₈ H ₂₅ F ₃ N ₂ O ₅ S
315790	OCF3	H	CH2CH2Ac	C ₂₈ H ₂₃ F ₃ N ₂ O ₆ S
315791	F	H	Bu	C ₂₇ H ₂₅ FN ₂ O ₄ S
315792	F	H	CH2CH2Ac	C ₂₇ H ₂₃ FN ₂ O ₅ S
315793	H	F	Bu	C ₂₇ H ₂₅ FN ₂ O ₄ S

SOURCE – Ajinomoto.

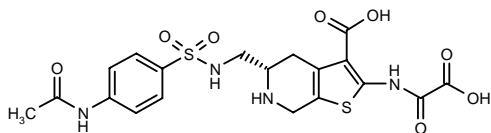
REFERENCES

1. Ikawa, H. et al. (Ajinomoto Co., Inc.) *Acylsulfonamide derivs.* WO 0202517.

315913

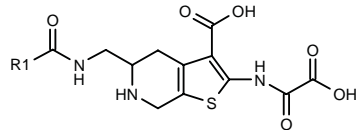
5(S)-(4-Acetamidophenylsulfonamidomethyl)-2-(oxaloamino)-4,5,6,7-tetrahydrothieno[2,3-c]pyridine-3-carboxylic acid

N-[5(S)-(4-Acetamidophenylsulfonamidomethyl)-3-carboxy-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl]oxamic acid



C19 H20 N4 O8 S2; Mol wt: 496.5190

ACTION – Protein-tyrosine-phosphatase inhibitor, particularly active against PTP1B (IC₅₀ = 0.13 μM). Potentially useful for the treatment of type 1 and type 2 diabetes, impaired glucose tolerance, insulin resistance and obesity, as well as other PTP-mediated conditions including immune diseases, coagulation dysfunctions, allergy, osteoporosis, proliferative diseases such as cancer and psoriasis, Alzheimer’s disease, schizophrenia and disorders related to unregulated synthesis of hormones or cytokines. Other exemplified compounds are:



Compound	R1	Isomer	Formula
315921	Ph		C ₁₈ H ₁₇ N ₃ O ₆ S
315923	4-(PhCONH)-Ph		C ₂₅ H ₂₂ N ₄ O ₇ S
315925	4-Ph-Ph		C ₂₄ H ₂₁ N ₃ O ₆ S
315926	2-OH-4-EtO-Ph		C ₂₀ H ₂₁ N ₃ O ₆ S
315928	3-(PhO)-Ph	S	C ₂₄ H ₂₁ N ₃ O ₇ S
315930	4-(PhCONH)-Ph	S	C ₂₅ H ₂₂ N ₄ O ₇ S
315931	1-OH-2-Naph	S	C ₂₂ H ₁₉ N ₃ O ₇ S
315932	3-OH-2-Naph	S	C ₂₂ H ₁₉ N ₃ O ₇ S
315933	3-OH-7-MeO-2-Naph	S	C ₂₃ H ₂₁ N ₃ O ₈ S
315934	4-(PhO)-PhNH	S	C ₂₄ H ₂₂ N ₄ O ₇ S

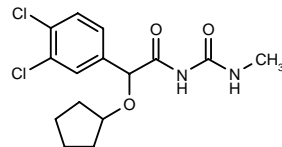
SOURCES – Novo Nordisk; Ontogen.

REFERENCES

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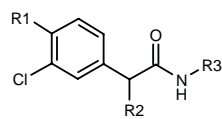
316595

N-[2-(Cyclopentyloxy)-2-(3,4-dichlorophenyl)acetyl]-N'-methylurea



C15 H18 Cl2 N2 O3; Mol wt: 345.2242

ACTION – Glucokinase activator with the ability to stimulate insulin secretion. Potentially useful for the treatment of type 2 diabetes. Other specifically claimed 2-phenyl-acetamide derivatives are:



Compound	R1	R2	R3	Formula
316596	Cl	cyclohexyl-O	CONHMe	C ₁₆ H ₂₀ Cl ₂ N ₂ O ₃
316597	Cl	2-cyclohexenyl-O	CONHMe	C ₁₆ H ₁₈ Cl ₂ N ₂ O ₃
316598	Cl	4-THP-O	CONHMe	C ₁₅ H ₁₈ Cl ₂ N ₂ O ₄
316599	SO ₂ Me	cyclopentyl-O	CONHMe	C ₁₆ H ₂₁ ClN ₂ O ₅ S
316600	SO ₂ Me	2-cyclohexenyl-O	CONHMe	C ₁₇ H ₂₁ ClN ₂ O ₅ S
316602	Cl	4-THP-O	2-thiazolyl	C ₁₆ H ₁₆ Cl ₂ N ₂ O ₃ S
316603	Cl	cyclopentyl-O	2-thiazolyl	C ₁₆ H ₁₆ Cl ₂ N ₂ O ₂ S
316604	Cl	cyclohexyl-O	2-thiazolyl	C ₁₇ H ₁₈ Cl ₂ N ₂ O ₂ S
316605	Cl	2-cyclohexenyl-O	2-thiazolyl	C ₁₇ H ₁₆ Cl ₂ N ₂ O ₂ S
316606	Cl	cyclopentyl-O	2-Pyr	C ₁₈ H ₁₈ Cl ₂ N ₂ O ₂
316607	SO ₂ Me	cyclopentyl-O	2-thiazolyl	C ₁₇ H ₁₉ ClN ₂ O ₄ S ₂
316608	SO ₂ Me	2-cyclohexenyl-O	4,5-dihydro-2-thiazolyl	C ₁₈ H ₂₁ ClN ₂ O ₄ S ₂
316609	Cl	cyclopentyl-CO	2-thiazolyl	C ₁₇ H ₁₆ Cl ₂ N ₂ O ₂ S
316610	Cl	cyclopentyl-SO ₂	2-thiazolyl	C ₁₆ H ₁₆ Cl ₂ N ₂ O ₃ S ₂
316611	Cl	cyclopentyl-S	2-thiazolyl	C ₁₆ H ₁₆ Cl ₂ N ₂ OS ₂

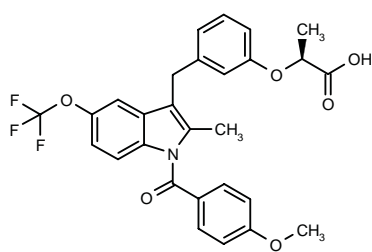
SOURCE – Roche.

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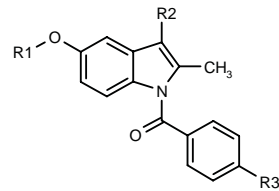
316666

2(S)-[3-[1-(4-Methoxybenzoyl)-2-methyl-5-(trifluoromethoxy)-1*H*-indol-3-ylmethyl]phenoxy]propionic acid



C28 H24 F3 N O6; Mol wt: 527.4926

ACTION – Peroxisome proliferator-activated receptor PPAR γ agonist, potentially useful for the treatment of type 2 diabetes, hyperglycemia, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, dyslipidemia, obesity and atherosclerosis. Other specifically claimed *N*-substituted indoles include the following:



Compound	R1	R2	R3	Formula
316668	Me	2-(CO ₂ HCH ₂ O)-PhCH ₂	Cl	C ₂₆ H ₂₂ ClNO ₅
316670	Me	4-[CO ₂ CH(Me)O]-PhCH ₂	Cl	C ₂₇ H ₂₄ ClNO ₅
316672	CF ₃	3-(CO ₂ HCH ₂ O)-PhCH ₂	OMe	C ₂₇ H ₂₂ F ₃ NO ₆
316674	CF ₃	(S)-2-[CO ₂ HCH(Me)O]-PhCH ₂	OMe	C ₂₈ H ₂₄ F ₃ NO ₆
316675	CF ₃	(R)-3-[CO ₂ HCH(Me)O]-PhCH ₂	OMe	C ₂₈ H ₂₄ F ₃ NO ₆
316676	CF ₃	3-[CO ₂ HC(Me)O]-PhCH ₂	OMe	C ₂₉ H ₂₆ F ₃ NO ₆
316677	CF ₃	(S)-3-[CO ₂ HCH(Me)O]-Ph	OMe	C ₂₇ H ₂₂ F ₃ NO ₆

SOURCE – Merck & Co.

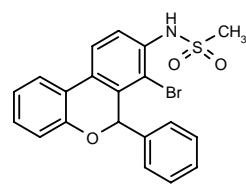
REFERENCES

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A-216054

317942

N-(7-Bromo-6-phenyl-6*H*-dibenzo[*b,d*]pyran-8-yl)-methanesulfonamide



C20 H16 Br N O3 S; Mol wt: 430.3204

ACTION – Selective nonsteroidal glucocorticoid receptor antagonist, potentially useful for the treatment of type 2 diabetes.

SOURCES – Abbott; Karo Bio.

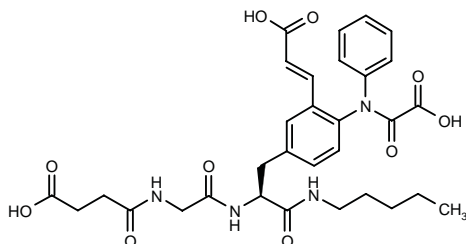
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1. Hartandi, K. et al. *Discovery of a chromene-based series of non-steroidal glucocorticoid receptor selective antagonists*. 223rd ACS Natl Meet (April 7-11, Orlando) 2002, Abst MEDI 58.

A-364504

317830

N-(3-Carboxypropionyl)-glycyl-3-(2-carboxyvinyl)-4-(2-hydroxy-*N*-phenyloxalamido)-*N*¹-pentyl-L-phenylalaninamide



C31 H36 N4 O10; Mol wt: 624.6434

ACTION – Potent, selective and competitive inhibitor of protein-tyrosine-phosphatase PTP1B, potentially useful for the treatment of type 2 diabetes.

SOURCE – Abbott.

REFERENCES

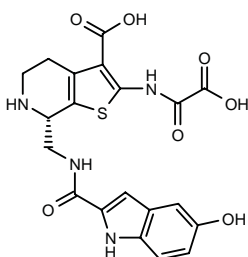
1. Liu, G. et al. *Discovery of competitive potent, and selective protein tyrosine phosphatase 1B inhibitors*. 223rd ACS Natl Meet (April 7-11, Orlando) 2002, Abst MEDI 2.

NNC-52-1246²⁻⁵

317828

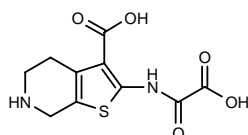
7(*S*)-(5-Hydroxy-1*H*-indol-2-ylcarboxamidomethyl)-2-(oxaloamino)-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine-3-carboxylic acid

N-[3-Carboxy-7(*S*)-(5-hydroxy-1*H*-indol-2-ylcarboxamidomethyl)-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridin-2-yl]oxamic acid



C20 H18 N4 O7 S; Mol wt: 458.4492

ACTION – Potent and highly selective, nonpeptide protein-tyrosine-phosphatase PTP1B inhibitor ($K_i = 0.29 \mu\text{M}$), potentially useful for the treatment of diabetes. Another related compound is:



NNC-52-0956 [317827]^{1,3-6}; C10 H10 N2 O5 S

SOURCES – Novo Nordisk; Ontogen.

REFERENCES

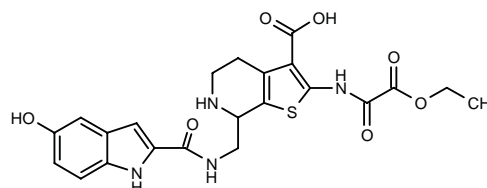
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2. Andersen, H.S. et al. (Ontogen Corp.;Novo Nordisk A/S) *Modulators of protein tyrosine phosphatases (PTPases)*. WO 0204459.
3. Andersen, H.S. et al. (Ontogen Corp.;Novo Nordisk A/S) *Modulators of protein tyrosine phosphatases (PTPases)*. WO 9946267.
4. Richter, L.S. et al. (Novo Nordisk A/S;Ontogen Corp.) *Modulators of protein tyrosine phosphatases*. WO 9946237.
5. Hansen, T.K. et al. *Potent non-peptide protein-tyrosine phosphatase inhibitors*. 223rd ACS Natl Meet (April 7-11, Orlando) 2002, Abst MEDI 3.
6. Iversen, L.F. et al. *Structure-based design of a low molecular weight, nonphosphorus, nonpeptide, and highly selective inhibitor of protein-tyrosine phosphatase 1B*. J Biol Chem 2000, 275(14): 10300.

OC-297963

315939

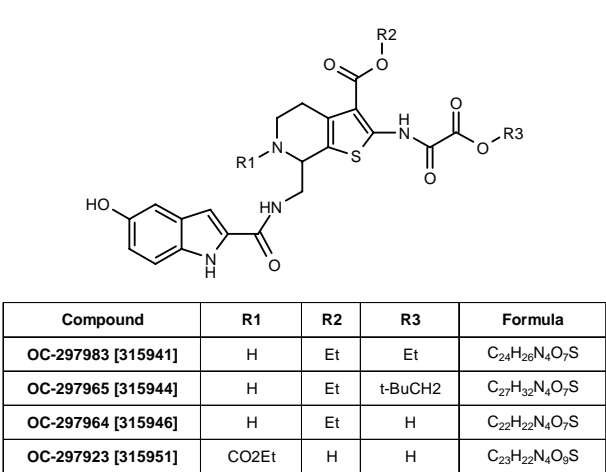
2-Ethoxalamido-7-(5-hydroxy-1*H*-indol-2-ylcarboxamidomethyl)-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine-3-carboxylic acid

N-[3-Carboxy-7-(5-hydroxy-1*H*-indol-2-ylcarboxamidomethyl)-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridin-2-yl]oxamic acid ethyl ester



C22 H22 N4 O7 S; Mol wt: 486.5028

ACTION – Protein-tyrosine-phosphatase inhibitor, particularly active against PTP1B ($\text{IC}_{50} = 0.063 \mu\text{M}$). Potentially useful for the treatment of type 1 and type 2 diabetes, impaired glucose tolerance, insulin resistance and obesity, as well as other PTP-mediated conditions including immune diseases, coagulation dysfunctions, allergy, osteoporosis, proliferative diseases such as cancer and psoriasis, Alzheimer's disease, schizophrenia and disorders related to unregulated synthesis of hormones or cytokines. Other exemplified compounds are:



SOURCES – Novo Nordisk; Ontogen.

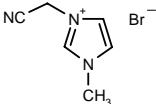
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TREATMENT OF DIABETIC COMPLICATIONS

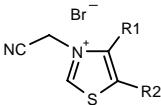
316501

3-(Cyanomethyl)-1-methyl-1*H*-imidazol-3-ium bromide



C6 H8 Br N3; Mol wt: 202.0542

ACTION – Agent capable of inhibiting the formation of advanced glycosylation end products (AGEs), potentially useful for improving myocardial elasticity in heart failure, as well as for reducing wrinkles, treating diabetes, kidney damage, damage to blood vasculature, hypertension, retinopathy, cataracts, peripheral neuropathy and osteoarthritis, and for preventing damage to tissues in the intra-peritoneal cavity caused by elevated levels of reducing sugars. Other exemplified cyanomethyl-substituted thiazolidinium and imidazolidinium compounds are:



Compound	R1	R2	Formula
316502	Me	Me	C ₇ H ₉ BrN ₂ S
316503	-(CH2)4-		C ₉ H ₁₁ BrN ₂ S
316504	-(CH2)3-		C ₈ H ₉ BrN ₂ S

SOURCE – Alteon.

REFERENCES

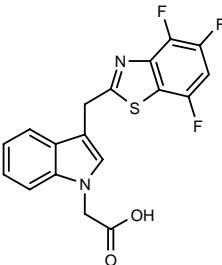
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LIDORESTAT*

292696

3-(4,5,7-Trifluorobenzothiazol-2-ylmethyl)-1*H*-indole-1-acetic acid

EML-676
IDD-000676-01
IDD-676



C18 H11 F3 N2 O2 S; Mol wt: 376.3569

ACTION – Potent and selective inhibitor of aldose reductase (IC₅₀ = 5 nM against human enzyme) with > 5,000-fold selectivity over human aldehyde reductase. In streptozotocin-diabetic rats, compound reduced sorbitol levels in nerve and lens (ED₅₀ = 1.9 and 4.5 mg/kg/day, respectively); it also improved motor nerve conduction velocity in a 3-month rat intervention model at 5 mg/kg/day over 2 months. Compound is currently undergoing clinical trials as a treatment for diabetic neuropathy.

SOURCES – Institute for Diabetes Discovery; Merck KGaA.

REFERENCES

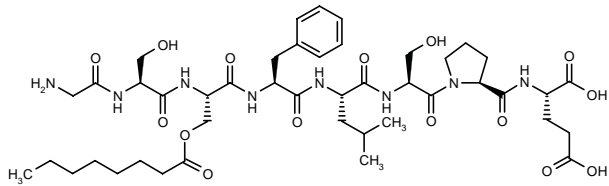
1. Jones, M.L. et al. (The Institutes for Pharmaceutical Discovery, Inc.) *Substd. indolealkanoic acids*. US 6214991, WO 9950268.
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*Identified compound **292696** Drug Data Rep 2000, 022(11): 1009.

TREATMENT OF GROWTH HORMONE SECRETION DISORDERS

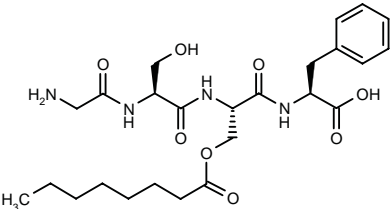
316544

Glycyl-L-seryl-3-*O*-octanoyl-L-seryl-L-phenylalanyl-L-leucyl-L-seryl-L-prolyl-L-glutamic acid



C44 H68 N8 O15; Mol wt: 949.0622

ACTION – Growth hormone (GH)-releasing peptide antagonist shown to reduce plasma GH levels in rats (1.40 ± 0.32 ng/ml vs. 10.11 ± 1.6 ng/ml in control animals) following s.c. administration at a dose of 300 mg/kg. Potentially useful for the treatment of acromegaly. Another exemplified peptide is:



316548: C25 H38 N4 O8

SOURCE – Zentaris.

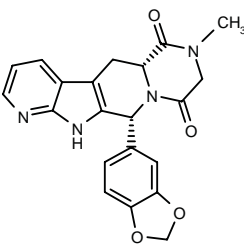
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TREATMENT OF MALE SEXUAL DYSFUNCTION

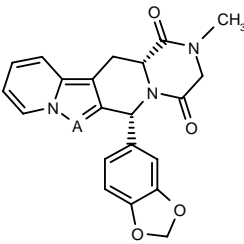
315104

(5a*R*,11*R*)-11-(1,3-Benzodioxol-5-yl)-7-methyl-5,5a,6,7,8,9,11,12-octahydropyrido[3'':2'':4',5']pyrrolo-[3',2':4,5]pyrido[1,2-*a*]pyrazine-6,9-dione

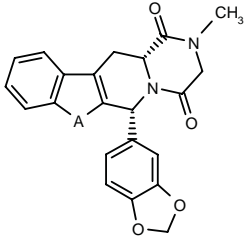


C21 H18 N4 O4; Mol wt: 390.3972

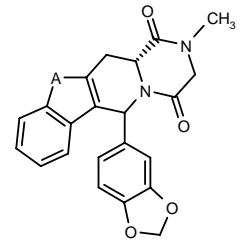
ACTION – Phosphodiesterase type 5 (PDE5) inhibitor (IC₅₀ = 2.3 nM), potentially useful for the treatment of erectile dysfunction and female arousal disorder, as well as other PDE5-mediated conditions including angina, hypertension, chronic obstructive pulmonary disease, acute respiratory distress syndrome, congestive heart failure, renal failure, atherosclerosis, vascular disorders, inflammatory diseases, stroke, bronchitis, myocardial infarction, asthma, allergic rhinitis, glaucoma, peptic ulcer, osteoporosis, preterm labor and irritable bowel syndrome, among others. Other specifically claimed compounds are:



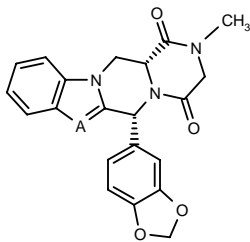
Compound	A	Formula
315105	CH	C ₂₂ H ₁₉ N ₃ O ₄
315106	N	C ₂₁ H ₁₈ N ₄ O ₄



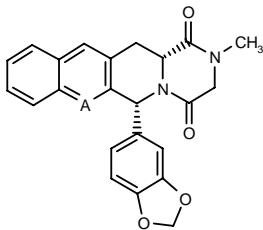
Compound	A	Formula
315108	S	C ₂₂ H ₁₈ N ₂ O ₄ S
315129	O	C ₂₂ H ₁₈ N ₂ O ₅



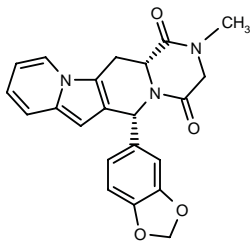
Compound	A	Isomer	Formula
315110	NH	R	C ₂₂ H ₁₉ N ₃ O ₄
315111	NH	S	C ₂₂ H ₁₉ N ₃ O ₄
315112	O	R	C ₂₂ H ₁₈ N ₂ O ₅
315114	S	R	C ₂₂ H ₁₈ N ₂ O ₄ S



Compound	A	Formula
315117	N	C ₂₁ H ₁₈ N ₄ O ₄
315120	CH	C ₂₂ H ₁₉ N ₃ O ₄



Compound	A	Formula
315126	CH	C ₂₄ H ₂₀ N ₂ O ₄
315127	N	C ₂₃ H ₁₉ N ₃ O ₄



315124: C22 H19 N3 O4

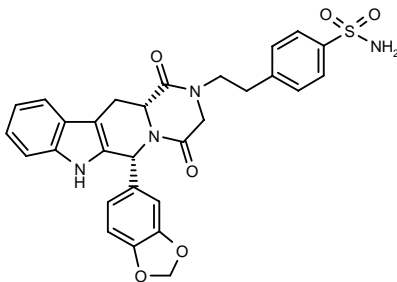
SOURCE – Lilly Icos.

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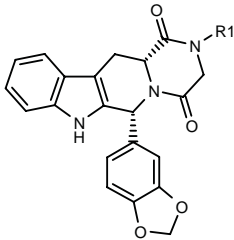
315135

4-[2-[(6*R*,12*aR*)-6-(1,3-Benzodioxol-5-yl)-1,4-dioxo-1,2,3,4,6,7,12,12*a*-octahydropyrazino[1',2':1,6]pyrido-[3,4-*b*]indol-2-yl]ethyl]benzenesulfonamide



C29 H26 N4 O6 S; Mol wt: 558.6124

ACTION – Phosphodiesterase type 5 (PDE5) inhibitor (IC₅₀ = 0.0014 μM), potentially useful for the treatment of erectile dysfunction and female arousal disorder, as well as other PDE5-mediated conditions including angina, hypertension, chronic obstructive pulmonary disease, acute respiratory distress syndrome, congestive heart failure, renal failure, atherosclerosis, vascular disorders, inflammatory diseases, stroke, bronchitis, myocardial infarction, asthma, allergic rhinitis, glaucoma, peptic ulcer, osteoporosis, preterm labor and irritable bowel syndrome, among others. Other exemplified compounds are:



Compound	R1	Formula
315136	OMe	C ₂₂ H ₁₉ N ₃ O ₅
315137	NH2	C ₂₁ H ₁₈ N ₄ O ₄

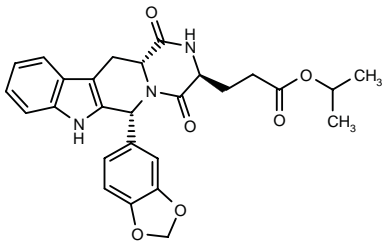
SOURCE – Lilly Icos.

REFERENCES

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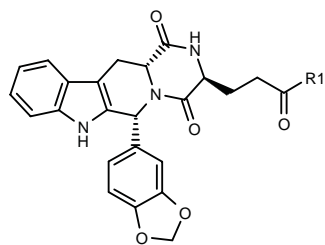
316813

3-[(3*S*,6*R*,12*aR*)-6-(1,3-Benzodioxol-5-yl)-1,4-dioxo-1,2,3,4,6,7,12,12*a*-octahydropyrazino[1',2':1,6]pyrido-[3,4-*b*]indol-3-yl]propionic acid isopropyl ester



C27 H27 N3 O6; Mol wt: 489.5253

ACTION – Phosphodiesterase type 5 (PDE5) inhibitor (IC₅₀ = 0.2 nM), potentially useful for the treatment of male erectile dysfunction and female sexual arousal disorders. Its use in the treatment of angina pectoris, hypertension, chronic obstructive pulmonary disease, acute respiratory distress syndrome, congestive heart failure, atherosclerosis, stroke, inflammation, asthma, bronchitis, glaucoma, allergic rhinitis, osteoporosis, etc., is also described. Other exemplified fused heterocyclic compounds include the following:



Compound	R1	Formula
316815	NH2	C ₂₄ H ₂₂ N ₄ O ₅
316817	t-BuO	C ₂₈ H ₂₉ N ₃ O ₆
316818	OH	C ₂₄ H ₂₁ N ₃ O ₆

SOURCE – Lilly Icos.

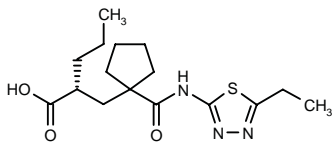
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TREATMENT OF FEMALE SEXUAL DYSFUNCTION

315364

2(R)-[1-[N-(5-Ethyl-1,3,4-thiadiazol-2-yl)carbamoyl]cyclopentylmethyl]pentanoic acid



C16 H25 N3 O3 S; Mol wt: 339.4575

ACTION – A compound from a series of cyclopentyl carboxamides that acts as an inhibitor of neutral endopeptidase (NEP) and was shown to enhance the pelvic nerve-stimulated increase in genital blood flow following either i.v. or topical administration in a rabbit model of sexual arousal. Potentially useful for the treatment of female sexual dysfunction, particularly female sexual arousal disorder.

SOURCE – Pfizer.

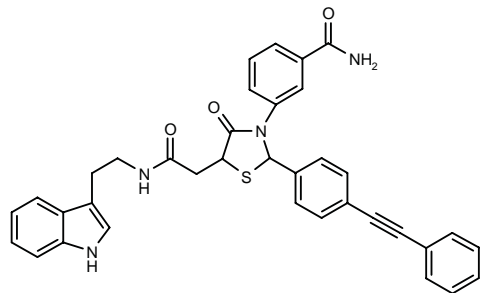
REFERENCES

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AGENTS FOR FEMALE INFERTILITY

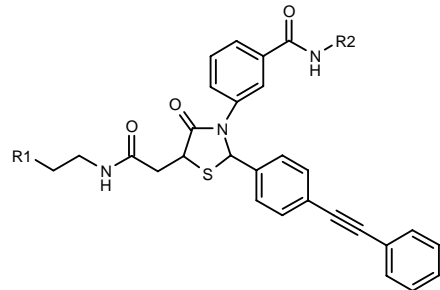
316962

3-[5-[N-[2-(1 H-Indol-3-yl)ethyl]carbamoylmethyl]-4-oxo-2-[4-(phenylethynyl)phenyl]thiazolidin-3-yl]benzamide

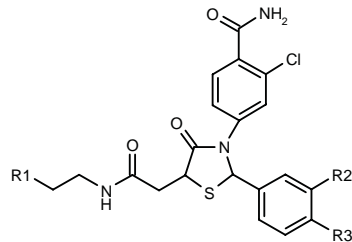


C36 H30 N4 O3 S; Mol wt: 598.7240

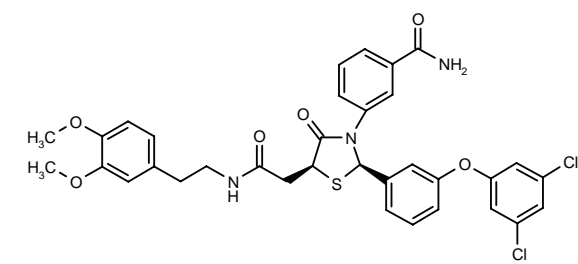
ACTION – Follicle-stimulating hormone (FSH) receptor agonist, reported to stimulate follicle maturation and induce ovulation. Potentially useful in *in vitro* fertilization applications. Other specifically claimed thiazolidin-4-one derivatives derivatives include the following:



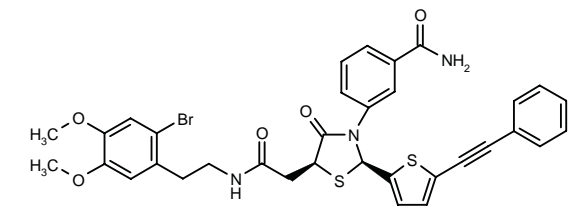
Compound	R1	R2	Isomer	Formula
316963	5-MeO-3-indolyl	H	2R	C ₃₇ H ₃₂ N ₄ O ₄ S
316964	6-F-3-indolyl	H	2R	C ₃₆ H ₂₉ FN ₄ O ₃ S
316966	2-Br-4,5-(MeO)2-Ph	CH2CH2OH	2R,5S	C ₃₈ H ₃₆ BrN ₃ O ₆ S
316968	1,3-benzodioxol-5-yl	H	2R,5S	C ₃₅ H ₂₉ N ₃ O ₅ S



Compound	R1	R2	R3	Isomer	Formula
316965	3-indolyl	Cl	Cl	2R	C ₂₈ H ₂₃ Cl ₃ N ₄ O ₃ S
316970	3,4-(MeO)2-Ph	H	allyl-O		C ₃₁ H ₃₂ ClN ₃ O ₆ S



316967: C34 H31 Cl2 N3 O6 S



316969: C34 H30 Br N3 O5 S2

SOURCE – Affymax.

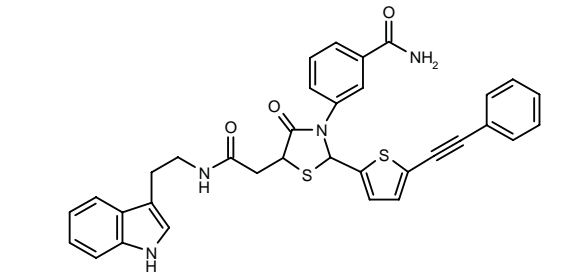
REFERENCES

1. Scheuerman, R.A. et al. (Affymax, Inc.) Agonists of follicle stimulating hormone activity. WO 0209706.

CONTRACEPTIVES

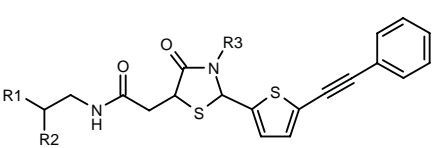
316941

3-[5-[N-[2-(1*H*-Indol-3-yl)ethyl]carbamoylmethyl]-4-oxo-2-[5-(phenylethynyl)thien-2-yl]thiazolidin-3-yl]benzamide



C34 H28 N4 O3 S2; Mol wt: 604.7522

ACTION – An antagonist of follicle-stimulating hormone (FSH) receptors that inhibits follicle maturation and ovulation. Potentially useful for contraception, endometriosis, endocrine hormone-dependent tumors and uterine fibroids. Other specifically claimed thiazolidin-4-one derivatives include the following:



Compound	R1	R2	R3	Formula
316942	2-thienyl	H	3-(NH2CO)-Ph	C ₃₀ H ₂₅ N ₃ O ₃ S ₃
316943	2-Cl-Ph	H	3-(NH2CO)-Ph	C ₃₂ H ₂₆ ClN ₃ O ₃ S ₂
316944	4-F-Ph	H	3-(NH2CO)-Ph	C ₃₂ H ₂₆ FN ₃ O ₃ S ₂
316945	4-Cl-Ph	H	3-(NH2CO)-Ph	C ₃₂ H ₂₆ ClN ₃ O ₃ S ₂
316946	1-cyclohexenyl	H	3-(NH2CO)-Ph	C ₃₂ H ₃₁ N ₃ O ₃ S ₂
316947	Ph	Me	3-(NH2CO)-Ph	C ₃₃ H ₂₉ N ₃ O ₃ S ₂
316948	2-F-Ph	H	3-(NH2CO)-Ph	C ₃₂ H ₂₆ FN ₃ O ₃ S ₂
316949	cyclohexyl	Me	3-(NH2CO)-Ph	C ₃₃ H ₃₅ N ₃ O ₃ S ₂
316950	4-Br-Ph	H	(R)-CH2CH(CONH2)-NHCO2Et	C ₃₁ H ₃₁ BrN ₄ O ₅ S ₂
316951	4-F-Ph	H	CH2CH2CONH2	C ₂₈ H ₂₆ FN ₃ O ₃ S ₂
316952	2-thienyl	H	(CH2)3CONH2	C ₂₇ H ₂₇ N ₃ O ₃ S ₃
316955	3-indolyl	H	CH2CH2CONH2	C ₃₀ H ₂₈ N ₄ O ₃ S ₂
316956	4-Br-Ph	H	CH2CH2CONH2	C ₂₈ H ₂₆ BrN ₃ O ₃ S ₂

SOURCE – Affymax.

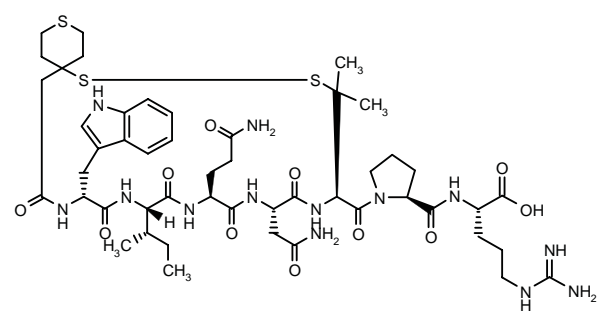
REFERENCES

1. Scheuerman, R.A. et al. (Affymax, Inc.) Agonists of follicle stimulating hormone activity. WO 0209705.

UTERINE STIMULANTS AND TOCOLYTICS

315489

N-[2-(4-Sulfanyltetrahydrothiopyran-4-yl)acetyl]-D-tryptophyl-L-isoleucyl-L-glutaminy-L-asparaginyl-L-penicillaminy-L-prolyl-L-arginine cyclic disulfide



C49 H73 N13 O11 S3; Mol wt: 1116.3940

ACTION – Oxytocin antagonist shown to reduce oxytocin-induced contractions in rat uterine preparations with an IC₅₀ of 31.8 nM, displaying 27-fold selectivity over vasopressin receptors in rat abdominal aorta preparations. Potentially useful for the treatment of preterm labor.

SOURCES – Daicel; Mitsubishi Pharma.

REFERENCES

1. Inoue, T. et al. (Daicel Chemical Industries, Ltd.; Mitsubishi-Tokyo Pharmaceuticals, Inc.) Peptide cpd. and pharmaceutical compsns. and medicines containing the same as the active ingredient. WO 0200688.

DERMATOLOGIC DRUGS

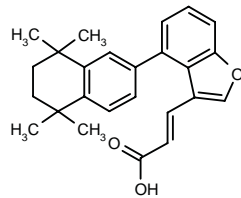
ANTIPSORIATICS

GW-0791

317799

3-[4-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)-1-benzofuran-3-yl]-2-propenoic acid

GW-0791X



C25 H26 O3; Mol wt: 374.4774

ACTION – Potent retinoid X receptor (RXR) agonist with nanomolar activity and more than 1,000-fold selectivity over retinoic acid RARα and other nuclear receptors. Potentially useful for the treatment of psoriasis.

SOURCE – GlaxoSmithKline.

REFERENCES

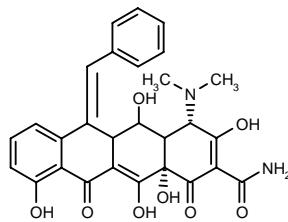
1. Miller, A.B. et al. *Structure based design of a potent RXR agonist*. 223rd ACS Natl Meet (April 7-11, Orlando) 2002, Abst MEDI 6.

ANTIINFECTIVE THERAPY

ANTIBIOTICS

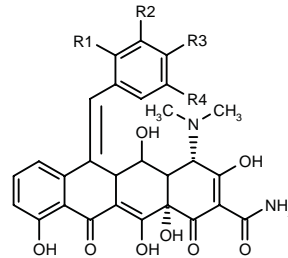
316020

6-Benzylidene-4(S)-(dimethylamino)-3,5,10,12,12a(S)-pentahydroxy-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydro-tetracene-2-carboxamide



C28 H26 N2 O8; Mol wt: 518.5194

ACTION – Antibacterial tetracycline, particularly useful for the treatment of *Escherichia coli*, *Staphylococcus aureus* and *Enterococcus faecalis* infections. Other exemplified 13-substituted methacycline compounds include the following:



Compound	R1	R2	R3	R4	Formula
316021	H	H	F	H	C ₂₈ H ₂₅ FN ₂ O ₈
316022	H	H	Me	H	C ₂₉ H ₂₈ N ₂ O ₈
316023	H	H	CF ₃	H	C ₂₉ H ₂₅ F ₃ N ₂ O ₈
316024	H	F	H	F	C ₂₈ H ₂₄ F ₂ N ₂ O ₈
316025	F	H	F	H	C ₂₈ H ₂₄ F ₂ N ₂ O ₈
316026	H	H	H	NO ₂	C ₂₈ H ₂₅ N ₃ O ₁₀
316027	H	H	OE _t	H	C ₃₀ H ₃₀ N ₂ O ₉
316028	Cl	H	H	H	C ₂₈ H ₂₅ ClN ₂ O ₈

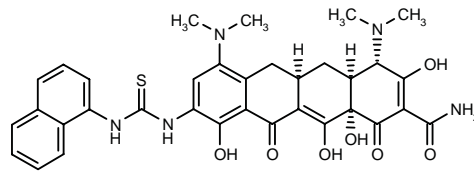
SOURCES – Paratek Pharmaceuticals; Tufts University, Boston, MA (US).

REFERENCES

1. Nelson, M.L. et al. (Paratek Pharmaceuticals, Inc.;Tufts University) *13-Substd. methacycline cpds*. WO 0204405.

316029

(4S,4aS,5aR,12aS)-4,7-Bis(dimethylamino)-3,10,12,12a-tetrahydroxy-9-[3-(1-naphthyl)thioureido]-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide



C34 H35 N5 O7 S; Mol wt: 657.7445

ACTION – Antibacterial tetracycline, particularly useful for the treatment of *Escherichia coli*, *Staphylococcus aureus* and *Enterococcus faecalis* infections. Other exemplified 9-substituted minocycline compounds include the following:

DERMATOLOGIC DRUGS

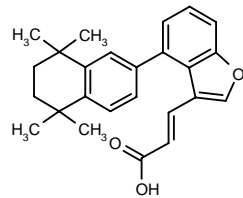
ANTIPSORIATICS

GW-0791

317799

3-[4-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)-1-benzofuran-3-yl]-2-propenoic acid

GW-0791X



C25 H26 O3; Mol wt: 374.4774

ACTION – Potent retinoid X receptor (RXR) agonist with nanomolar activity and more than 1,000-fold selectivity over retinoic acid RARα and other nuclear receptors. Potentially useful for the treatment of psoriasis.

SOURCE – GlaxoSmithKline.

REFERENCES

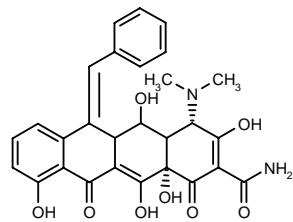
1. Miller, A.B. et al. *Structure based design of a potent RXR agonist*. 223rd ACS Natl Meet (April 7-11, Orlando) 2002, Abst MEDI 6.

ANTIINFECTIVE THERAPY

ANTIBIOTICS

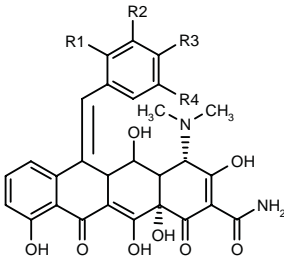
316020

6-Benzylidene-4(S)-(dimethylamino)-3,5,10,12,12a(S)-pentahydroxy-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydro-tetracene-2-carboxamide



C28 H26 N2 O8; Mol wt: 518.5194

ACTION – Antibacterial tetracycline, particularly useful for the treatment of *Escherichia coli*, *Staphylococcus aureus* and *Enterococcus faecalis* infections. Other exemplified 13-substituted methacycline compounds include the following:



Compound	R1	R2	R3	R4	Formula
316021	H	H	F	H	C ₂₈ H ₂₅ FN ₂ O ₈
316022	H	H	Me	H	C ₂₉ H ₂₈ N ₂ O ₈
316023	H	H	CF3	H	C ₂₉ H ₂₅ F ₃ N ₂ O ₈
316024	H	F	H	F	C ₂₈ H ₂₄ F ₂ N ₂ O ₈
316025	F	H	F	H	C ₂₈ H ₂₄ F ₂ N ₂ O ₈
316026	H	H	H	NO2	C ₂₈ H ₂₅ N ₃ O ₁₀
316027	H	H	OEt	H	C ₃₀ H ₃₀ N ₂ O ₉
316028	Cl	H	H	H	C ₂₈ H ₂₅ ClN ₂ O ₈

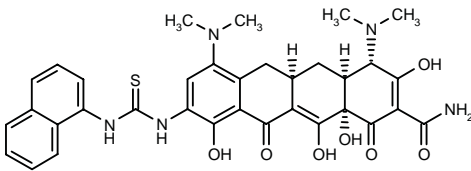
SOURCES – Paratek Pharmaceuticals; Tufts University, Boston, MA (US).

REFERENCES

1. Nelson, M.L. et al. (Paratek Pharmaceuticals, Inc.;Tufts University) *13-Substd. methacycline cpds*. WO 0204405.

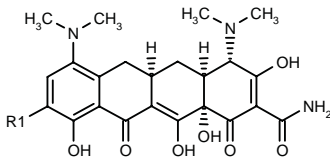
316029

(4S,4aS,5aR,12aS)-4,7-Bis(dimethylamino)-3,10,12,12a-tetrahydroxy-9-[3-(1-naphthyl)thioureido]-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide



C34 H35 N5 O7 S; Mol wt: 657.7445

ACTION – Antibacterial tetracycline, particularly useful for the treatment of *Escherichia coli*, *Staphylococcus aureus* and *Enterococcus faecalis* infections. Other exemplified 9-substituted minocycline compounds include the following:



Compound	R1	Formula
316030	NHCONHPh	C ₃₀ H ₃₃ N ₅ O ₈
316032	NHCOSPh	C ₃₀ H ₃₂ N ₄ O ₆ S
316034	3,5-(CF ₃) ₂ -PhNHCSNH	C ₃₂ H ₃₁ F ₆ N ₅ O ₇ S
316036	1-cyclopentenyl-ethynyl	C ₃₀ H ₃₃ N ₃ O ₇
316038	1,3-benzodioxol-5-yl-CH ₂ NH	C ₃₁ H ₃₄ N ₄ O ₉
316039	i-BuNHCH ₂	C ₂₈ H ₃₈ N ₄ O ₇
316040	4-Br-PhOCONHCH ₂	C ₃₁ H ₃₃ BrN ₄ O ₉
316041	CH ₂ NHCO ₂ C ₅ H ₁₁	C ₃₀ H ₄₀ N ₄ O ₉
316042	4-(CF ₃ O)-PhNHCONHCH ₂	C ₃₂ H ₃₄ F ₃ N ₅ O ₉

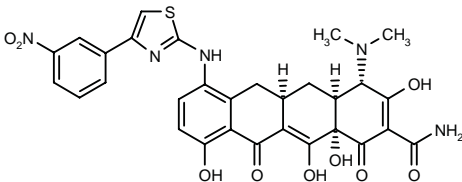
SOURCES – Paratek Pharmaceuticals; Tufts University, Boston, MA (US).

REFERENCES

1. Nelson, M.L. et al. (Paratek Pharmaceuticals, Inc.;Tufts University) *9-Substd. minocycline cpds.*. WO 0204406.

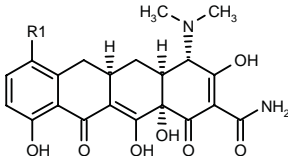
316044

(4*S*,4*aS*,5*aR*,12*aS*)-4-(Dimethylamino)-3,10,12,12*a*-tetrahydroxy-7-[4-(3-nitrophenyl)thiazol-2-ylamino]-1,11-dioxo-1,4,4*a*,5,5*a*,6,11,12*a*-octahydrotetracene-2-carboxamide



C30 H27 N5 O9 S; Mol wt: 633.6353

ACTION – Antibacterial tetracycline, particularly useful for the treatment of *Escherichia coli*, *Staphylococcus aureus* and *Enterococcus faecalis* infections. Other exemplified 7-substituted tetracycline compounds include the following:



Compound	R1	Formula
316045	3-MeO-PhCH ₂ CH ₂	C ₃₀ H ₃₂ N ₂ O ₈
316046	3-[N(Me) ₂ CH ₂]-Ph	C ₃₀ H ₃₃ N ₃ O ₇
316047	3-(4-morpholinyl-CH ₂)-Ph	C ₃₂ H ₃₆ N ₃ O ₈
316048	2-Pyr-CH ₂ CO	C ₂₈ H ₂₇ N ₃ O ₈
316049	3-(i-PrOCO)-Ph	C ₃₁ H ₃₂ N ₂ O ₉
316050	2-MeO-5-[CO ₂ EtCH(i-Pr)NHCH ₂]-Ph	C ₃₆ H ₄₃ N ₃ O ₁₀
316051	2-MeO-5-[N(Me) ₂ CH ₂ CH ₂ NHCH ₂]-Ph	C ₃₃ H ₄₀ N ₄ O ₈
316052	4-(PhCH ₂ NHCH ₂)-Ph	C ₃₆ H ₃₅ N ₃ O ₇

SOURCES – Paratek Pharmaceuticals; Tufts University, Boston, MA (US).

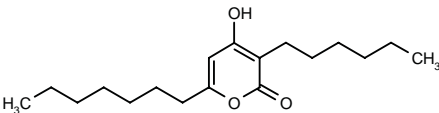
REFERENCES

1. Nelson, M.L. et al. (Paratek Pharmaceuticals, Inc.;Tufts University) *7-Substd. tetracycline cpds.* WO 0204407.

SCH-419560

317192

6-Heptyl-3-hexyl-4-hydroxy-2*H*-pyran-2-one



C18 H30 O3; Mol wt: 294.4320

ACTION – Antibiotic isolated from the fermentation broth of *Pseudomonas fluorescens*, with MIC₅₀ values of 2.5 and > 64 µg/ml against *Staphylococcus aureus* and *Escherichia coli*, respectively. However, in *E. coli* constitutively overexpressing the *rpoE* gene essential for viability of the bacteria, the compound was much more active, with an MIC₅₀ value of 5 µg/ml.

SOURCE – Schering-Plough.

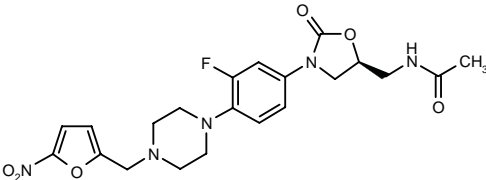
REFERENCES

1. Chu, M. et al. *Structure of Sch 419560, a novel α-pyrone antibiotic produced by Pseudomonas fluorescens.* J Antibiot 2002, 55(2): 215.

ANTIBACTERIAL DRUGS

316064

N-[3-[3-Fluoro-4-[4-(5-nitrofuran-2-ylmethyl)piperazin-1-yl]phenyl]-2-oxooxazolidin-5(*S*)-ylmethyl]acetamide



C21 H24 F N5 O6; Mol wt: 461.4476

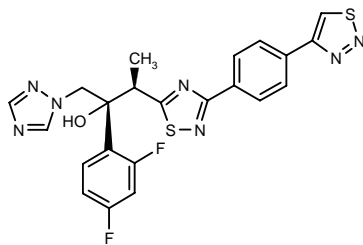
ACTION – Oxazolidinone antibacterial agent effective against Gram-positive bacteria including drug-resistant staphylococci and enterococci, as well as anaerobic bacteria such as *Mycobacterium tuberculosis* and other *Mycobacterium* species. It gave MIC values of 2 µg/ml or less against a panel of Gram-positive bacteria *in vitro* and was also shown to be effective *in vivo* against methicillin-resistant *Staphylococcus aureus* MRSA 562 after oral administration, with activity comparable to that of linezolid. Another exemplified compound is:

ANTIFUNGAL AGENTS

RO-098246*

312179

2(*R*)-(2,4-Fluorophenyl)-3(*R*)-[3-[4-(1,2,3-thiadiazol-4-yl)phenyl]-1,2,4-thiadiazol-5-yl]-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol



C22 H17 F2 N7 O S2; Mol wt: 497.5523

ACTION – Antifungal agent with broad-spectrum activity including *Candida albicans* (MIC = 0.0025-0.098 µg/ml), *Candida glabrata* (MIC = 0.003-0.0038 µg/ml), *Cryptococcus neoformans* (MIC = 0.019 µg/ml) and *Aspergillus fumigatus* (MIC = 0.037-0.11 µg/ml). Compound showed better antifungal activity than ravuconazole against all species tested including fluconazole-resistant *Candida*. In addition, it inhibited cytochrome P-450 CYP3A4 to a lesser extent than ravuconazole, suggesting reduced drug–drug interactions.

SOURCE – Basilea Pharmaceutica.

REFERENCES

1. Komiyama, S. et al. (Basilea Pharmaceutica AG) *Azole derivs.* US 6319933, WO 0179196.

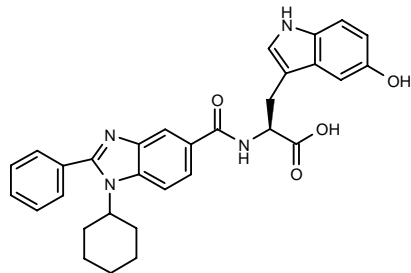
2. Komiyama, S. et al. *Parallel synthesis of azole antifungals and identification of novel thiadiazole-containing antifungals.* 223rd ACS Natl Meet (April 7-11, Orlando) 2002, Abst MEDI 175.

*Identified compound **312179** Drug Data Rep 2002, 024(02): 0161.

ANTIVIRAL DRUGS

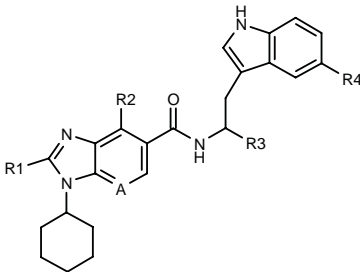
315581

N-(1-Cyclohexyl-2-phenyl-1*H*-benzimidazol-5-ylcarbonyl)-5-hydroxy-L-tryptophan

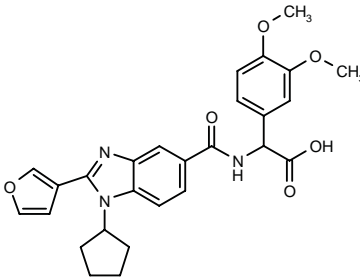


C31 H30 N4 O4; Mol wt: 522.6020

ACTION – Agent with the ability to inhibit viral RNA polymerases, particularly hepatitis C virus (HCV) NS5B polymerase (IC₅₀ < 1 µM). Potentially useful for the treatment of HCV infection. Other exemplified compounds are:



Compound	R1	R2	R3	R4	A	Isomer	Formula
315583	2-Pyr	H	CO2H	OH	N	S	C ₂₉ H ₂₈ N ₆ O ₄
315585	3-furyl	Me	CO2H	OCH2CO2H	CH	S	C ₃₂ H ₃₂ N ₄ O ₇
315586	3-furyl	H	H	OH	CH		C ₂₈ H ₂₈ N ₄ O ₃
315587	2-Pyr	H	CO2Me	OCH2CO2H	CH	S	C ₃₃ H ₃₃ N ₅ O ₆



315582: C27 H27 N3 O6

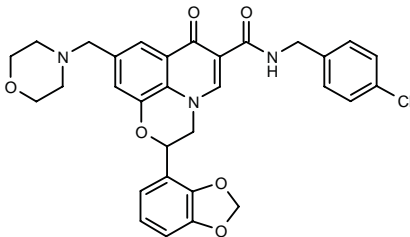
SOURCE – Boehringer Ingelheim.

REFERENCES

1. Beaulieu, P.L. et al. (Boehringer Ingelheim (Canada) Ltd.) *Viral polymerase inhibitors.* WO 0204425.

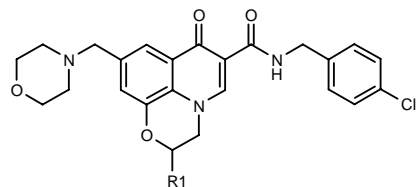
315628

2-(1,3-Benzodioxol-4-yl)-*N*-(4-chlorobenzyl)-9-(morpholin-4-ylmethyl)-7-oxo-3,7-dihydro-2*H*-[1,4]oxazino[2,3,4-*ij*]-quinoline-6-carboxamide



C31 H28 Cl N3 O6; Mol wt: 574.0302

ACTION – Antiviral oxoquinolone that inhibits viral DNA polymerase (IC₅₀ = 0.20 µM against cytomegalovirus DNA polymerase). Potentially useful as an antiherpesvirus agent, particularly against cytomegalovirus infections. Other exemplified compounds are:



Compound	R1	Formula
315629	1-Me-2-imidazolyl-SCH2	C ₂₉ H ₃₀ ClN ₅ O ₄ S
315631	2-Pyr	C ₂₉ H ₂₇ ClN ₄ O ₄
315633	3-Pyr	C ₂₉ H ₂₇ ClN ₄ O ₄
315634	3-OH-Ph	C ₃₀ H ₂₈ ClN ₃ O ₅

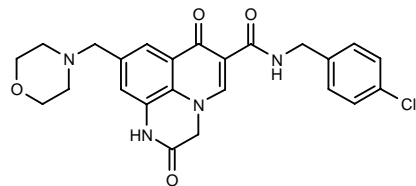
SOURCE – Pharmacia.

REFERENCES

1. Thaisrivongs, S. et al. (Pharmacia Corp.) *Oxazinoquinolones useful for the treatment of viral infections*. WO 0204462.

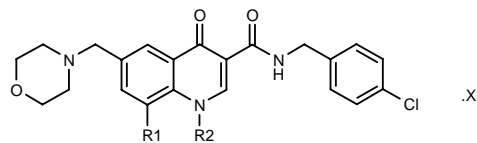
315954

N-(4-Chlorobenzyl)-9-(morpholin-4-ylmethyl)-2,7-dioxo-1,2,3,7-tetrahydropyrido[1,2,3-*de*]quinoxaline-6-carboxamide



C24 H23 Cl N4 O4; Mol wt: 466.9227

ACTION – Antiviral agent, particularly useful against herpesviruses. Compound inhibited human cytomegalovirus, varicella-zoster virus and herpes simplex virus polymerases with respective IC₅₀ values of 3, 0.06 and < 0.51 μM. Other exemplified heterocyclic carboxamides are:



Compound	R1,R2	X	Formula
315955	-NHCO-		C ₂₃ H ₂₁ ClN ₄ O ₄
315956	-NHCOCH(Me)-	HBr	C ₂₅ H ₂₅ ClN ₄ O ₄ ·HBr
315957	-NHCOCH2CH2-		C ₂₅ H ₂₅ ClN ₄ O ₄
315958	-N=C(NHCH2Ph)CH2-		C ₃₁ H ₃₀ ClN ₅ O ₃

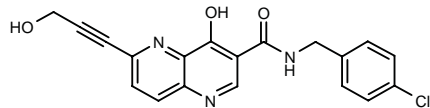
SOURCE – Pharmacia.

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1. Anderson, D.J. et al. (Pharmacia Corp.) *Heterocycle carboxamides as antiviral agents*. WO 0204445.

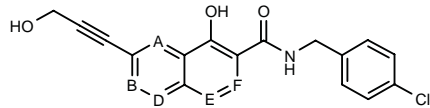
315959

N-(4-Chlorobenzyl)-4-hydroxy-6-(3-hydroxy-1-propynyl)-1,5-naphthyridine-3-carboxamide



C19 H14 Cl N3 O3; Mol wt: 367.7906

ACTION – Antiviral agent that inhibits human cytomegalovirus polymerase and is thus expected to be useful against herpesviruses. Other exemplified heterocyclic carboxamides are:



Compound	A	B	D	E	F	Formula
315961	N	N	CH	N	CH	C ₁₈ H ₁₃ ClN ₄ O ₃
315963	CH	CH	CH	CH	N	C ₂₀ H ₁₅ ClN ₂ O ₃
315964	CH	CH	N	CH	N	C ₁₉ H ₁₄ ClN ₃ O ₃

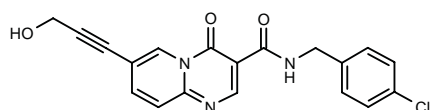
SOURCE – Pharmacia.

REFERENCES

1. Schnute, M.E. et al. (Pharmacia Corp.) *Heterocycle carboxamides as antiviral agents*. WO 0204422, WO 0204443.

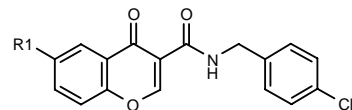
315966

N-(4-Chlorobenzyl)-7-(3-hydroxy-1-propynyl)-4-oxo-4H-pyrido[1,2-*a*]pyrimidine-3-carboxamide

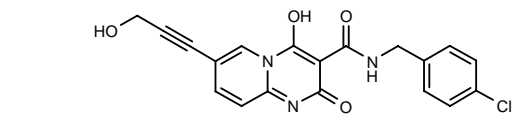


C19 H14 Cl N3 O3; Mol wt: 367.7906

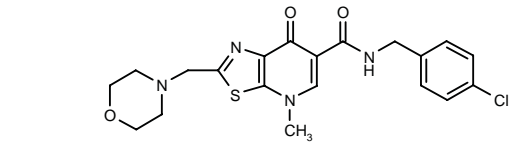
ACTION – Antiviral agent that inhibits human cytomegalovirus polymerase and is thus expected to be useful against herpesviruses. Other exemplified heterocyclic carboxamides are:



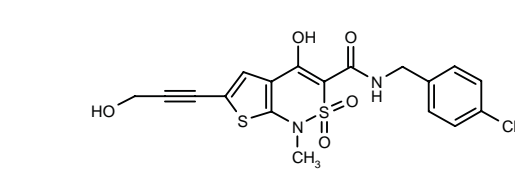
Compound	R1	Formula
315968	ethynylene-CH2OH	C ₂₀ H ₁₄ ClNO ₄
315974	4-morpholinyl-CH2	C ₂₂ H ₂₁ ClN ₂ O ₄
315975	(R)-3-OH-1-pyrrolidinyl-CH2	C ₂₂ H ₂₁ ClN ₂ O ₄



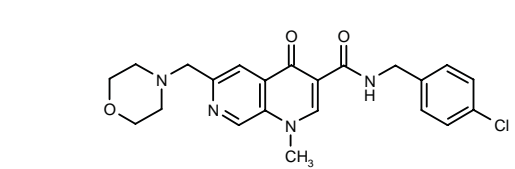
315967: C19 H14 Cl N3 O4



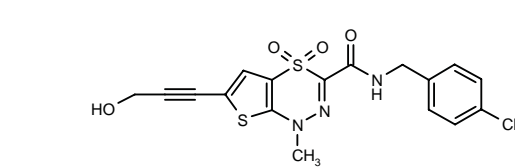
315969: C20 H21 Cl N4 O3 S



315970: C18 H15 Cl N2 O5 S2



315972: C22 H23 Cl N4 O3



315973: C17 H14 Cl N3 O4 S2

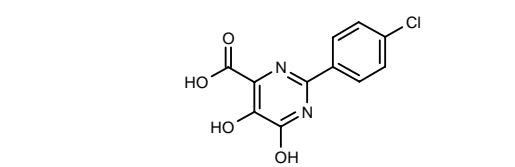
SOURCE – Pharmacia.

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1. Bundy, G.L. et al. (Pharmacia Corp.) *Heterocycle carboxamides as antiviral agents*. WO 0204444.

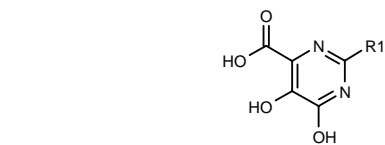
316151

2-(4-Chlorophenyl)-5,6-dihydroxypyrimidine-4-carboxylic acid



C11 H7 Cl N2 O4; Mol wt: 266.6393

ACTION – Antiviral agent with the ability to inhibit hepatitis C virus (HCV) RNA-dependent RNA polymerase (NS5B), and thus potentially useful for the treatment of HCV infection. Other exemplified dihydroxypyrimidine carboxylic acids are:



Compound	R1	Formula
316152	2-(2-Cl-PhCH2NHCONH)-Ph	C19H15ClN4O5
316154	3-[(Ph)2CHNHCONH]-Ph	C25H20N4O5
316155	2-[2,4,6-(Cl)3-PhSO2NH]-Ph	C17H10Cl3N3O6S
316156	2-thienyl	C9H6N2O4S
316157	3-(2-Cl-PhCH2NHCONH)-2-thienyl	C17H13ClN4O5S
316158	4-(2-Cl-PhCH2NHCONH)-3-thienyl	C17H13ClN4O5S
316159	4-(1-Naph-SO2NHCONH)-3-thienyl	C20H14N4O7S2
316161	(E)-3-(PhCH=CH)-2-thienyl	C17H12N2O4S

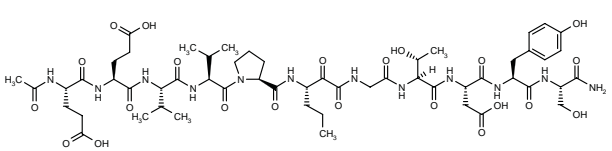
SOURCE – Istituto di Ricerche di Biologia Molecolare P. Angeletti, Pomezia (IT).

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1. Gardelli, C. et al. (Istituto di Ricerche di Biologia Molecolare P. Angeletti SpA) *Dihydroxypyrimidine carboxylic acids as viral polymerase inhibitors*. WO 0206246.

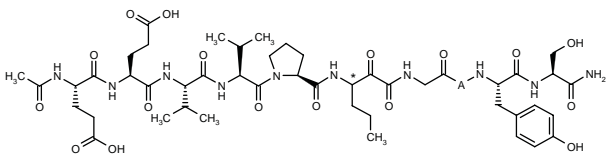
316622

N-Acetyl-L-glutamyl-L-glutamyl-L-valyl-L-valyl-L-prolyl-[3(*S*)-amino-2-oxohexanoyl]-glycyl-L-threonyl-L-aspartyl-L-tyrosyl-L-serinamide



C55 H82 N12 O22; Mol wt: 1263.3150

ACTION – Hepatitis C virus (HCV) NS3 serine protease inhibitor ($K_i = 2.7$ nM), potentially useful for the treatment of HCV infection. Other exemplified peptides are:



Compound	A	* Isomer	Formula
316625	-L-Met-L-Ser-		C55H84N12O20S
316626	-L-Thr-L-Ser-	S	C54H82N12O21
316627	-L-Thr-L-His-	S	C57H84N14O20
316628	-4-S-oxo-L-Met-L-Asp-	S	C56H84N12O22S

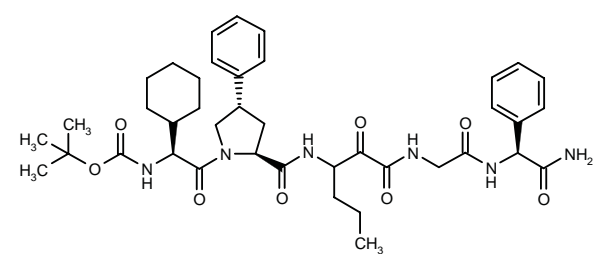
SOURCE – Corvas.

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1. Lim-Wilby, M. et al. (Corvas International, Inc.) *Novel peptides as NS3-serine protease inhibitors of hepatitis C virus*. WO 0208251.

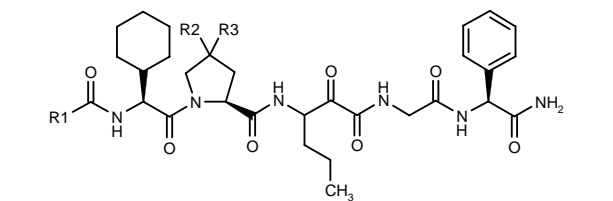
316631

N-(*tert*-Butoxycarbonyl)-L-cyclohexylglycyl-4(*S*)-phenyl-L-prolyl-(3-amino-2-oxohexanoyl)-glycyl-L-phenylglycinamide

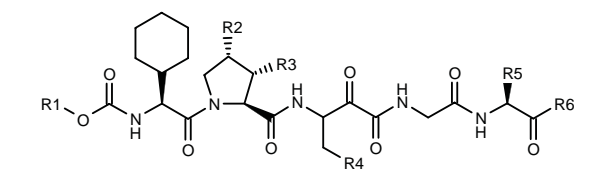


C40 H54 N6 O8; Mol wt: 746.9006

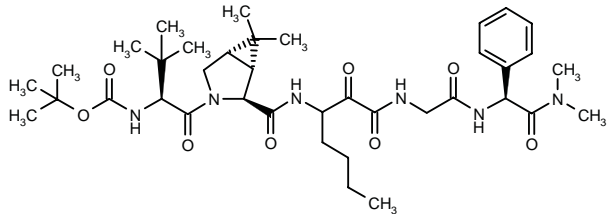
ACTION – Hepatitis C virus (HCV) NS3 serine protease inhibitor, potentially useful for the treatment of HCV infection. Other specifically claimed peptides include the following:



Compound	R1	R2,R3	Formula
316633	i-BuO	-OCH2CH2O-	C ₃₆ H ₅₂ N ₆ O ₁₀
316634	2-CO2H-3,4-(Cl)2-Ph	-S(CH2)3S-	C ₄₀ H ₄₈ Cl ₂ N ₆ O ₉ S ₂
316635	i-BuO	-SCH2CH2S-	C ₃₆ H ₅₂ N ₆ O ₉ S ₂



Compound	R1	R2	R3	R4	R5	R6	Formula
316637	i-Bu	H	allyl	cyclopropyl	Ph	OH	C ₃₈ H ₅₃ N ₅ O ₉
316638	t-Bu	Ph	H	Et	cyclohexyl	OH	C ₄₀ H ₅₉ N ₅ O ₉
316640	i-Bu	NHSO2Ph	H	Et	Ph	NH2	C ₄₀ H ₅₅ N ₇ O ₁₀ S



316639: C38 H58 N6 O8

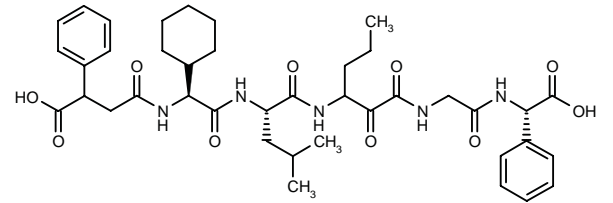
SOURCES – Corvas; Schering-Plough.

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1. Saksena, A.K. et al. (Schering Corp.;Corvas International, Inc.) *Novel peptides as NS3-serine protease inhibitors of hepatitis C virus*. WO 0208244.

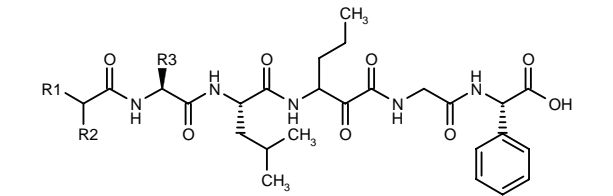
316706

N-(3-Carboxy-3-phenylpropionyl)-L-cyclohexylglycyl-L-leucyl-(3-amino-2-oxohexanoyl)-glycyl-L-phenylglycine

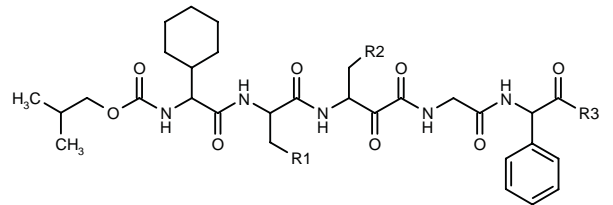


C40 H53 N5 O10; Mol wt: 763.8837

ACTION – Antiviral agent, an inhibitor of hepatitis C virus (HCV) NS3 serine protease ($K_i < 100$ nM). Other exemplified peptides include the following:



Compound	R1	R2	R3	Formula
316708	H	CH2CH(Ph)CO2H	cyclohexyl	C ₄₁ H ₅₅ N ₅ O ₁₀
316709	H	CH(CO2H)Bu	cyclohexyl	C ₃₈ H ₅₇ N ₅ O ₁₀
316712	i-Bu	NHSO2Me	cyclopentyl	C ₃₆ H ₅₆ N ₆ O ₁₀ S



Compound	R1	R2	R3	Formula
316710	1,3-dithiolan-2-yl	Et	OH	C ₃₅ H ₅₁ N ₅ O ₉ S ₂
316711	cyclopropyl	Et	OH	C ₃₅ H ₅₁ N ₅ O ₉
316713	cyclopropyl	cyclopropyl	OH	C ₃₆ H ₅₁ N ₅ O ₉
316714	cyclopropyl	cyclopropyl	NH2	C ₃₆ H ₅₂ N ₆ O ₈
316715	cyclopropyl	cyclopropyl	NHOMe	C ₃₇ H ₅₄ N ₆ O ₉

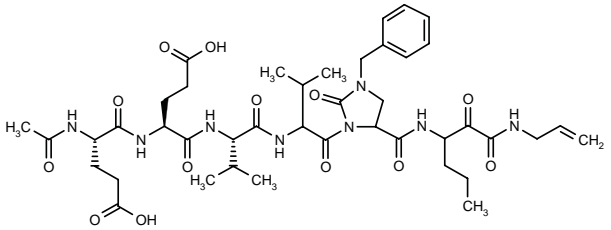
SOURCES – Corvas; Schering-Plough.

REFERENCES

1. Saksena, A.K. et al. (Schering Corp.;Corvas International, Inc.) *Novel peptides as NS3-serine protease inhibitors of hepatitis C virus*. WO 0208187.

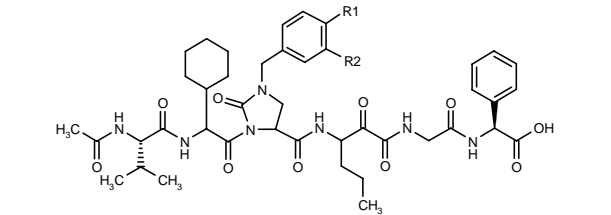
316726

N-Acetyl-L-glutamyl-L-glutamyl-L-valine 1-[5-[*N*-[1-(allylaminooxalyl)butyl]carbamoyl]-3-benzyl-2-oxoimidazolidin-1-ylcarbonyl]-2-methylpropylamide

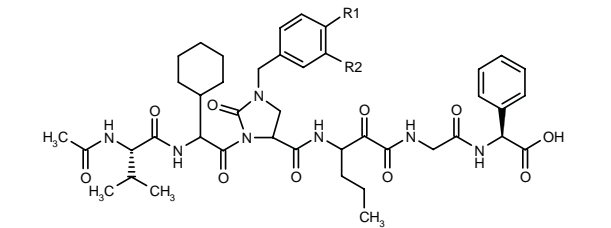


C42 H60 N8 O13; Mol wt: 884.9790

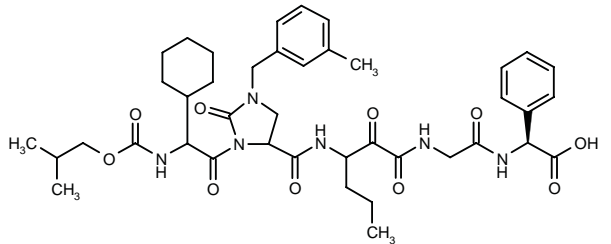
ACTION – Antiviral agent, an inhibitor of hepatitis C virus (HCV) NS3 serine protease ($K_i < 1000$ nM). Other exemplified imidazolidinones include the following:



Compound	R1	R2	Formula
316732	H	H	C ₄₄ H ₆₂ N ₈ O ₁₅
316733	Cl	Cl	C ₄₄ H ₆₀ Cl ₂ N ₈ O ₁₅



Compound	R1	R2	Formula
316734	H	H	C ₄₂ H ₅₅ N ₇ O ₁₀
316737	Me	Me	C ₄₄ H ₅₉ N ₇ O ₁₀
316739	H	Me	C ₄₃ H ₅₇ N ₇ O ₁₀
316740	Me	H	C ₄₃ H ₅₇ N ₇ O ₁₀
316742	H	OMe	C ₄₃ H ₅₇ N ₇ O ₁₁
316743	OMe	H	C ₄₃ H ₅₇ N ₇ O ₁₁
316744	t-Bu	H	C ₄₆ H ₆₃ N ₇ O ₁₀



316738: C41 H54 N6 O10

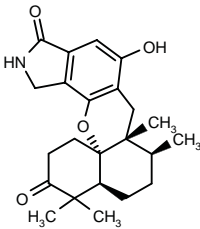
SOURCE – Schering-Plough.

REFERENCES

1. Arasappan, A. et al. (Schering Corp.) *Novel imidazolidinones as NS3-serine protease inhibitors of hepatitis C virus*. WO 0208198.

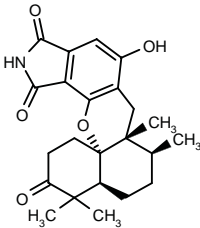
317279

(6*aR*,7*S*,9*aS*,13*aS*)-5-Hydroxy-6*a*,7,10,10-tetramethyl-2,3,6,6*a*,7,8,9,9*a*,10,11,12,13-dodecahydro-1*H*-naphtho[1',8':5,6]pyrano[2,3-*e*]isoindol-3,11-dione



C23 H29 N O4; Mol wt: 383.4851

ACTION – Antiviral agent, a derivative of stachyflin with comparable antiviral activity against influenza A virus (IC₅₀ = 6 and 3 nM, respectively) and lower cytotoxicity against uninfected cells (CC₅₀ = 98 and 65 μM, respectively). Another related compound is:



317280: C23 H27 N O5

SOURCE – Shionogi.

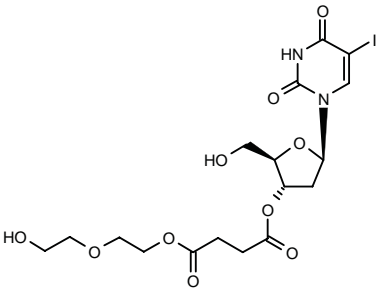
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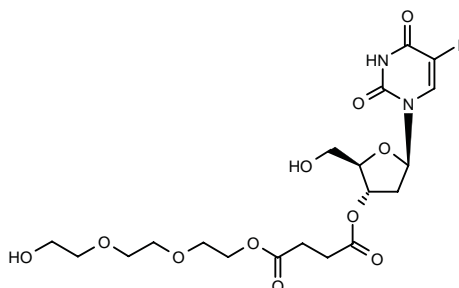
317330

2'-Deoxy-3'-*O*-[4-[2-(2-hydroxyethoxy)ethoxy]-4-oxo-butyryl]-5-iodouridine



C17 H23 I N2 O10; Mol wt: 542.2727

ACTION – Dermal prodrug of 5-iodo-2'-deoxyuridine (IDU; idoxuridine) with improved lipophilicity compared to the parent drug and good stability at pH 7.4. The prodrug was readily hydrolyzed to IDU by porcine esterase. Percutaneous absorption studies showed that the prodrug significantly increased the cumulative amounts of IDU that penetrate through excised human skin compared to the parent drug. Potentially useful for the treatment of herpes simplex virus keratitis. Another related prodrug is:



317331: C19 H27 I N2 O11

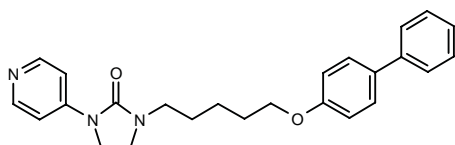
SOURCES – Università degli Studi di Catania, Catania (IT); Università di Napoli Federico II, Napoli (IT); Università degli Studi di Perugia, Perugia (IT); Università degli Studi di Sassari, Sassari (IT).

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1. Bonina, F.P. et al. *New oligoethylene ester derivatives of 5-iodo-2'-deoxyuridine as dermal prodrugs: Synthesis, physicochemical properties, and skin permeation studies.* J Pharm Sci 2002, 91(1): 171.

317909

1-[5-(Biphenyl-4-yloxy)pentyl]-3-(4-pyridyl)imidazolidin-2-one



C25 H27 N3 O2; Mol wt: 401.5073

ACTION – Antiviral agent active against picornaviruses, especially enterovirus 71 (EV 71; $IC_{50} = 0.04 \mu M$), with an excellent selectivity index (> 625) relative to human rhabdomyosarcoma cells, human normal skin fibroblast D551 cells and human normal lung fibroblast W138 cells. Potentially useful for the treatment of fatal infections caused by EV 71.

SOURCES – Chang Gung University, Taoyuan (TW); National Health Research Institutes, Taipei (TW).

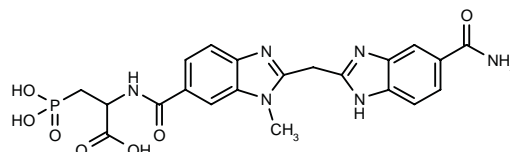
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APC-6336^{*,1,2}

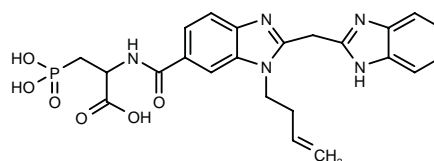
288687

2-[2-(5-Carbamoyl-1*H*-benzimidazol-2-ylmethyl)-1-methyl-1*H*-benzimidazol-6-ylcarboxamido]-3-phosphonopropionic acid



C21 H21 N6 O7 P; Mol wt: 500.4059

ACTION – Agent for the treatment of hepatitis C virus (HCV) infections, a potent and selective Zn^{2+} -dependent inhibitor of HCV NS3 serine protease ($IC_{50} = 0.20 \mu M$ in the presence of $5.0 \mu M Zn^{2+}$). Another related compound is:



318192²: C23 H24 N5 O6 P

SOURCES – Bristol-Myers Squibb; Celera Genomics.

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1. Hataye, J.M. et al. (Celera Genomics) *Novel cpds. and compsns. for treating hepatitis C infections.* WO 0020400.
2. Yeung, K.-S. et al. *Structure-activity relationship studies of the bisbenzimidazole-based Zn^{2+} -dependent inhibitor of hepatitis C virus NS3 serine protease, APC-6336.* 223rd ACS Natl Meet (April 7-11, Orlando) 2002, Abst MEDI 163.

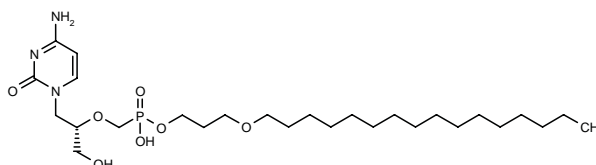
*Identified compound **288687** Drug Data Rep 2000, 022(08): 0725.

HDP-CDV

317302

[2-(4-Amino-2-oxo-1,2-dihydropyrimidin-1-yl)-1(*S*)-(hydroxymethyl)ethoxy]methylphosphonic acid 3-(hexadecyloxy)propyl monoester

Hexadecyloxypropyl-cidofovir



C27 H52 N3 O7 P; Mol wt: 561.6958

ACTION – Antiviral agent, an alkoxyalkyl ester of cidofovir with improved activity compared to the parent compound against human cytomegalovirus (CMV; EC_{50} = 0.002 and 460 nM, respectively). Compound was also active against herpes simplex virus type 2 (HSV-2; EC_{50} = 0.08 μ M), varicella-zoster virus (VZV; EC_{50} = 0.003 μ M), Epstein-Barr virus (EBV; EC_{50} < 0.1 μ M), human herpes virus type 6 and type 8 (HHV-6 and HHV-8; EC_{50} < 0.02 μ M), as well as variola, monkeypox, cowpox and vaccinia viruses. It was orally available in mice and provided plasma levels at least 10-fold higher than the EC_{50} values for the various poxviruses.

SOURCES – University of California, San Diego, La Jolla, CA (US); US Army Medical Research Institute of Infectious Diseases, Frederick, MD (US).

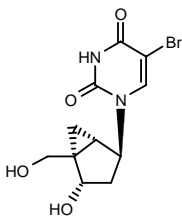
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- Winegarden, K.L. et al. *Oral pharmacokinetics and preliminary toxicology of 1-O-hexadecyloxypropyl-cidofovir in mice.* Antivir Res 2002, 53(3): Abst 105.
- First oral drug developed to treat smallpox infection.* DailyDrugNews.com (Daily Essentials) 2002, March 22.

(M)-MCdBrU

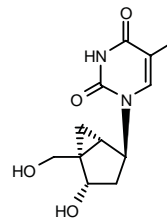
316464

5-Bromo-1-[(1S,2S,4S,5R)-4-hydroxy-5-(hydroxymethyl)-bicyclo[3.1.0]hex-2-yl]uracil



C11 H13 Br N2 O4; Mol wt: 317.1377

ACTION – Nucleoside analogue with antitumor and antiviral activity, displaying *in vitro* activity against a panel of viral strains including herpes simplex virus (HSV), varicella-zoster virus (VZV), Epstein-Barr virus (EBV) and cytomegalovirus (CMV), as well as vaccinia and poxviruses. Another exemplified 5-substituted pyrimidine derivative is:



(M)-MCdIU[316467]: C11 H13 I N2 O4

SOURCE – US Department of Health & Human Services (US).

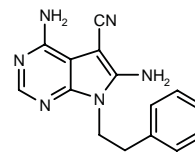
REFERENCES

- Marquez, V.E. and Russ, P.L. (US Department of Health & Human Services) *5-Subst. pyrimidine derivs. of conformationally locked nucleoside analogues.* WO 0208204.

UMJD-1369*

292518

4,6-Diamino-7-(2-phenylethyl)-7H-pyrrolo[2,3-d]-pyrimidine-5-carbonitrile



C15 H14 N6; Mol wt: 278.3176

ACTION – Pyrrolopyrimidine nucleoside analogue with antiviral activity against human cytomegalovirus (HCMV) and herpes simplex virus type 1 (HSV-1), giving respective IC_{50} values of 17 and 75 nM; it showed a good therapeutic index, with IC_{50} values of 35 and 160 μ M, respectively, for cytotoxicity in uninfected cells. Compound appeared to act at an early stage of viral replication and was shown to significantly inhibit the expression of the early gene product pUL57 and the late gene product pp150.

SOURCES – Università degli Studi di Bologna, Bologna (IT); Lake Erie College Osteopathic Medicine, Erie, PA (US); University of Michigan, Ann Arbor, MI (US).

REFERENCES

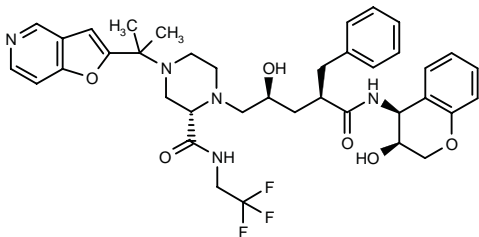
- Townsend, L.B. and Drach, J.C. (University of Michigan) *Pyrrolo[2,3-d]pyrimidines as antiviral agents.* WO 0042043.
- Nassiri, M.R. et al. *Activity of a new pyrrolopyrimidine nucleoside analog against human cytomegalovirus.* Antivir Res 2002, 53(3): Abst 86.

*Identified compound **292518** Drug Data Rep 2000, 022(11): 1015.

AIDS MEDICINES

305851

4-[1-(Furo[3,2-*c*]pyridin-2-yl)-1-methylethyl]-1-[2(*S*)-hydroxy-4(*R*)-[*N*-[3(*S*)-hydroxy-3,4-dihydro-2*H*-1-benzopyran-4(*S*)-yl]carbamoyl]-5-phenylpentyl]-*N*-(2,2,2-trifluoroethyl)piperazine-2(*S*)-carboxamide



C38 H44 F3 N5 O6; Mol wt: 723.7886

ACTION – Anti-HIV agent, an indinavir derivative with IC_{95} values of < 8 nM against the NL4-3 strain of HIV and IC_{95} values of 62-250 nM against indinavir-resistant strains. Compound showed favorable pharmacokinetics in dogs, with an oral bioavailability of 65%.

SOURCE – Merck & Co.

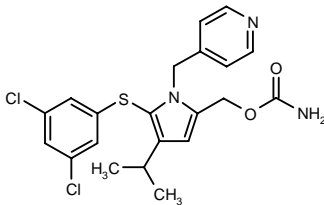
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1. Tata, J.R. et al. (Merck & Co., Inc.) *γ*-Hydroxy-2-(fluoroalkylaminocarbonyl)-1-piperazinepentanamides as HIV protease inhibitors. WO 0138332.

2. Duffy, J.L. et al. *Synthesis and activity of novel HIV protease inhibitors with improved potency against multiple PI-resistant viral strains*. 223rd ACS Natl Meet (April 7-11, Orlando) 2002, Abst MEDI 241.

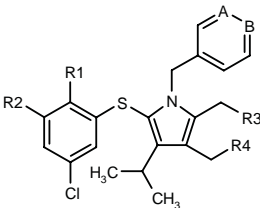
315396

Carbamic acid 5-(3,5-dichlorophenylsulfanyl)-4-isopropyl-1-(pyridin-4-ylmethyl)-1*H*-pyrrol-2-ylmethyl ester



C21 H21 Cl2 N3 O2 S; Mol wt: 450.3879

ACTION – An inhibitor of HIV reverse transcriptase (RT) displaying an IC_{50} of 33 nM against HIV-1 RT. It protected HIV-infected MT-4 cells with an IC_{50} of 16 nM. Other exemplified pyrrole derivatives are:



Compound	R1	R2	R3	R4	A	B	Formula
315398	H	Cl	H	OH	N	CH	C ₂₁ H ₂₂ Cl ₂ N ₂ OS
315399	Cl	H	H	OH	CH	N	C ₂₁ H ₂₂ Cl ₂ N ₂ OS
315401	H	Cl	H	N3	CH	N	C ₂₁ H ₂₁ Cl ₂ N ₅ S
315402	H	Cl	Me	OH	CH	N	C ₂₂ H ₂₄ Cl ₂ N ₂ OS
315403	H	Cl	OH	OH	CH	N	C ₂₁ H ₂₂ Cl ₂ N ₂ O ₂ S

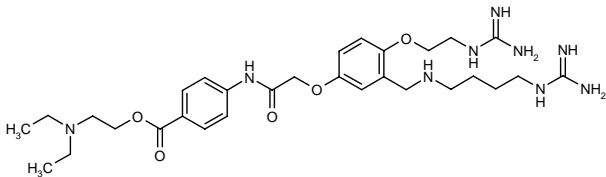
SOURCE – Roche.

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1. Dymock, B.W. et al. (F. Hoffmann-La Roche AG) *Pyrrole derivs. for treating AIDS*. WO 0202524.

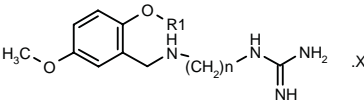
315749

4-[2-[3-(4-Guanidinobutylaminomethyl)-4-(2-guanidinoethoxy)phenoxy]acetamido]benzoic acid 2-(diethyl-amino)ethyl ester

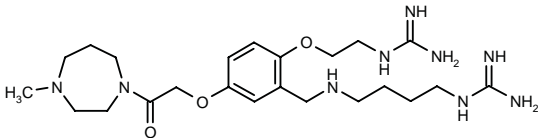


C30 H47 N9 O5; Mol wt: 613.7593

ACTION – Antiviral agent for the treatment of HIV infection, shown to inhibit the binding of the viral protein Tat to the RNA Tar binding site *in vitro*, with a K_i value below 1 μ M. Other exemplified aryl compounds are:



Compound	R1	n	X	Formula
315752	CH2CH2NHC(=NH)NH2	3		C ₁₅ H ₂₇ N ₇ O ₂
315754	CH2CH2NHC(=NH)NH2	5		C ₁₇ H ₃₁ N ₇ O ₂
315755	CH2CH2CH2NH2	4		C ₁₆ H ₂₉ N ₅ O ₂
315759	CH2-ethynylene-CH2NH2	4	.3CF3CO2H	C ₁₇ H ₂₇ N ₅ O ₂ .3C ₂ HF ₃ O ₂
315761	CH2CH2CH2NHCH2Ph	4		C ₂₃ H ₃₅ N ₅ O ₂



315762: C23 H41 N9 O3

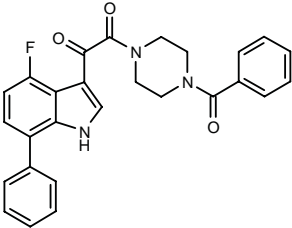
SOURCE – RiboTargets.

REFERENCES

1. Drysdale, M.J. et al. (RiboTargets Ltd.) *Aryl cpds., their preparation and their use in therapy.* WO 0200614.

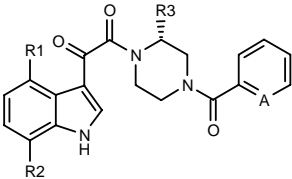
315860

1-(4-Benzoylpiperazin-1-yl)-2-(4-fluoro-7-phenyl-1*H*-indol-3-yl)ethane-1,2-dione



C27 H22 F N3 O3; Mol wt: 455.4868

ACTION – Anti-HIV agent shown to reduce HIV-1 infectivity in HeLa CD4 CCR5 cells with an EC₅₀ < 1 μM. Other exemplified piperazine derivatives include the following:



Compound	R1	R2	R3	A	Formula
315861	OMe	2-Pyr	H	CH	C ₂₇ H ₂₄ N ₄ O ₄
315862	F	2-(CO ₂ MeCH ₂)-5-tetrazolyl	H	CH	C ₂₅ H ₂₂ FN ₇ O ₅
315863	F	4-Pyr-NHCO	H	CH	C ₂₇ H ₂₂ FN ₅ O ₄
315864	F	CONHCH ₂ CH(OMe) ₂	H	CH	C ₂₆ H ₂₇ FN ₄ O ₆
315866	F	5-NH ₂ CO-1,2,4-oxadiazol-3-yl	H	CH	C ₂₄ H ₁₉ FN ₆ O ₅
315867	F	5-CF ₃ -1,2,4-oxadiazol-3-yl	Me	CH	C ₂₅ H ₁₉ F ₄ N ₆ O ₄
315868	F	5-CCl ₃ -1,2,4-oxadiazol-3-yl	Me	N	C ₂₄ H ₁₈ Cl ₃ FN ₆ O ₄
315869	F	5-(NH ₂ CH ₂)-1,2,4-oxadiazol-3-yl	H	CH	C ₂₄ H ₂₁ FN ₆ O ₄
315870	F	1,2,4-triazol-1-yl	H	CH	C ₂₃ H ₁₉ FN ₆ O ₃

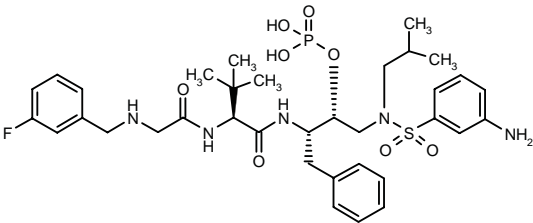
SOURCE – Bristol-Myers Squibb.

REFERENCES

1. Wallace, O.B. et al. (Bristol-Myers Squibb Co.) *Compsn. and antiviral activity of subst. indoleoxoacetic piperazine derivs.* WO 0204440.

316072

N-(3-Fluorobenzyl)glycyl-3-methyl-*L*-valine *N*-[3-[*N*-(3-aminophenylsulfonyl)-*N*-isobutylamino]-1(*S*)-benzyl-2(*R*)-(phosphonooxy)propyl]amide



C35 H49 F N5 O8 P S; Mol wt: 749.8371

ACTION – A representative compound from a series of phosphate esters of peptidomimetic compounds that act as HIV protease inhibitors. Potentially useful for the treatment of HIV infection, either alone or in combination with HIV reverse transcriptase inhibitors or other HIV protease inhibitors.

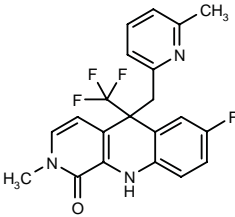
SOURCE – Bristol-Myers Squibb.

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1. Kaltenbach, R.F. III and Trainor, G.L. (DuPont Pharmaceuticals Co.) *Phosphate esters of bis-amino acid sulfonamides containing subst. benzyl amines.* WO 0206292.

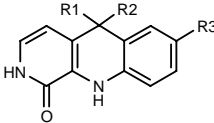
316568

7-Fluoro-2-methyl-5-(6-methylpyridin-2-ylmethyl)-5-(tri-fluoromethyl)-1,2,5,10-tetrahydrobenzo[*b*]-1,7-naphthyridin-1-one



C21 H17 F4 N3 O; Mol wt: 403.3773

ACTION – HIV reverse transcriptase inhibitor for the treatment of HIV infection. Other specifically claimed tricyclic compounds are:



Compound	R1	R2	R3	Formula
316569	CF3	2-Pyr-ethynylene	F	C ₂₀ H ₁₁ F ₄ N ₃ O
316570	CH ₂ OH	CF3	Cl	C ₁₄ H ₁₀ ClF ₃ N ₂ O ₂
316571	i-PrOCH ₂	CF3	Cl	C ₁₇ H ₁₆ ClF ₃ N ₂ O ₂
316572	cyclobutyl-OCH ₂	CF3	Cl	C ₁₈ H ₁₆ ClF ₃ N ₂ O ₂
316573	CN	Bu	Cl	C ₁₇ H ₁₆ ClN ₃ O
316574	CH ₂ CH ₂ NHEt	CF3	F	C ₁₇ H ₁₇ F ₄ N ₃ O
316576	i-PrNHCH ₂	CF3	F	C ₁₇ H ₁₇ F ₄ N ₃ O
316578	allyl-NHCH ₂	CF3	F	C ₁₇ H ₁₅ F ₄ N ₃ O
316579	cyclobutyl-NHCH ₂	CF3	F	C ₁₈ H ₁₇ F ₄ N ₃ O

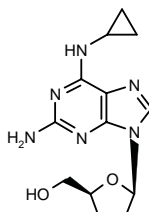
SOURCE – Bristol-Myers Squibb.

REFERENCES

1. Rodgers, J.D. et al. (DuPont Pharmaceuticals Co.) *Tricyclic 2-pyridone cpds. useful as HIV reverse transcriptase inhibitors*. WO 0208226.

317076

*N*⁶-Cyclopropyl-2',3'-didehydro-2',3'-dideoxyadenosine



C13 H16 N6 O2; Mol wt: 288.3094

ACTION – Anti-HIV-1 agent, a nucleoside reverse transcriptase inhibitor prodrug of 2',3'-didehydro-2',3'-dideoxyguanosine (DAG) with comparable antiviral activity in HIV-1-infected human leukemia MT-2 cells ($EC_{50} = 8.6 \mu M$) but improved solubility, lipophilicity and stability at pH 2 and 7.4 and lower cytotoxicity against uninfected MT-2 cells ($IC_{50} > 100 \mu M$).

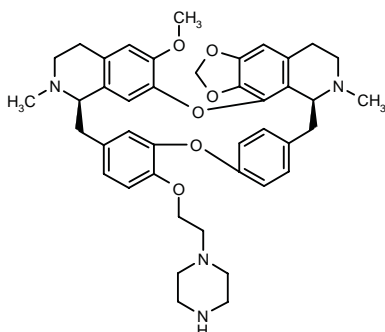
SOURCES – University of Georgia, Athens, GA (US); Yale University, New Haven, CT (US).

REFERENCES

1. Ray, A.S. et al. *Novel use of a guanosine prodrug approach to convert 2',3'-didehydro-2',3'-dideoxyguanosine into a viable antiviral agent*. Antimicrob Agents Chemother 2002, 46(3): 887.

317332

(14*S*,27*R*)-33-Methoxy-13,28-dimethyl-22-[2-(1-piperazinyl)ethyl]-2,5,7,20-tetraoxa-13,28-diazaoctacyclo-[25.6.2.2^{16,19}.1^{3,10}.1^{21,25}.0^{4,8}.0^{14,39}.0^{31,35}]nonatriaconta-1(33),3,8,10(39),16,18,21(38),22,24,31,34,36-dodecaene



C42 H48 N4 O6; Mol wt: 704.8632

ACTION – Anti-HIV-1 agent, a derivative of cepharanthine, an alkaloid isolated from the plant *Stephania cepharantha* Hayata, with antiinflammatory, antiallergic and immunomodulatory activity. The derivative exhibited higher activity than the parent compound against HIV-1 replication in chronically infected promonocytic U1 cells ($EC_{50} = 6$ and 46 nM , respectively). It was also significantly more selective as an inhibitor of HIV-1 replication compared to cepharanthine, with a selectivity index of 293 and 46, respectively.

SOURCE – Kaken.

REFERENCES

1. Baba, M. et al. *Anti-HIV-1 activity and structure-activity relationship of cepharanoline derivatives in chronically infected cells*. Antivir Chem Chemother 2001, 12(5): 307.

TREATMENT OF PROTOZOAL DISEASES

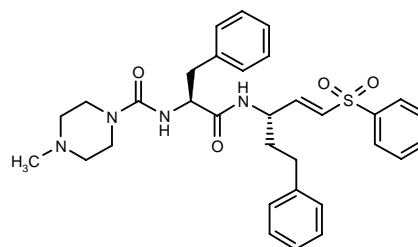
CRA-3316

282598

N-(4-Methylpiperazin-1-ylcarbonyl)-L-phenylalanine 1(*S*)-(2-phenylethyl)-3-(phenylsulfonyl)-2(*E*)-propenyl amide

APC-3316

K-11777



C32 H38 N4 O4 S; Mol wt: 574.7422

ACTION – Antiprotozoal agent, a potent and irreversible inhibitor of *Trypanosoma brucei* cysteine protease proven active *in vitro* against *T. brucei* ($IC_{50} = 0.1 \mu M$). *In vivo*, compound was effective in rescuing mice from lethal infection with *Trypanosoma cruzi*. No toxicity was seen in monkeys following treatment for 7 days with twice the proposed human dose.

SOURCES – Celera Genomics; Institute for OneWorld Health; National Institutes of Health, Bethesda, MD (US).

REFERENCES

1. Rasnick, D. et al. (Celera Genomics) *Irreversible cysteine protease inhibitors containing vinyl groups conjugated to electron withdrawing groups*. US 6287840.
2. Cummins, C.L. and Benet, L.Z. *Characterizing the transport of K-11777, a vinylsulfone peptidomimetic, and its metabolites across in vitro cell monolayers*. Annu Meet Am Assoc Pharm Sci (AAPS) (Nov 14-18, New Orleans) 1999, Abst.
3. Cummins, C.L. and Benet, L.Z. *Investigating the role of CYP3A4 and P-glycoprotein in the in vitro intestinal metabolism of K11777, a peptidomimetic cysteine protease inhibitor*. Annu Meet Am Assoc Pharm Sci (AAPS) (Oct 29-Nov 2, Indianapolis) 2000, Abst 4135.
4. Jacobsen, W. et al. *In vitro evaluation of the disposition of a novel cysteine protease inhibitor*. Drug Metab Dispos 2000, 28(11): 1343.

5. Jacobsen, W.M. et al. *Metabolism and adduct formation of K-11777, a novel cysteine protease inhibitor, in vitro (human and rat) and in vivo (rat)*. Annu Meet Am Assoc Pharm Sci (AAPS) (Nov 14-18, New Orleans) 1999, Abst.

6. Troeberg, L. et al. *Cysteine proteinase inhibitors kill cultured bloodstream forms of Trypanosoma brucei brucei*. Exp Parasitol 1999, 91(4): 349.

7. Ugele, B. et al. *Novel synthetic cysteine protease inhibitors suppress growth of human breast cancer cell lines*. J Cancer Res Clin Oncol 2001, 127(Suppl. 1): S43.

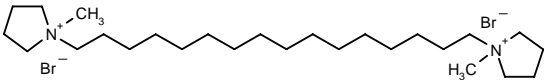
8. Wong, D.H. et al. *The effect of cathepsins B and L inhibition on tumor progression in the B16F10 experimental metastasis model*. Proc Amer Assoc Cancer Res 2001, 42: Abst 797.

9. *Potential therapeutic agent for Chagas' disease enters development*. DailyDrugNews.com (Daily Essentials) 2002, Feb 15.

G25

316877

1,1'-(Hexadecane-1,16-diyl)bis(1-methylpyrrolidinium) dibromide



C26 H54 Br2 N2; Mol wt: 554.5346

ACTION – Potent antimalarial agent that specifically attacks the parasite in infected erythrocytes by inhibiting phosphatidylcholine biosynthesis during asexual development within red blood cells. Compound was active *in vitro* against laboratory strains of *Plasmodium falciparum* including chloroquine-, quinine-, mefloquine- and pyrimethamine-resistant strains, with IC₅₀ values of 1-5.3 nM; it was not toxic to human lymphoblasts, macrophages or megakaryoblasts (IC₅₀ > 6 µM). In mice infected with *Plasmodium chabaudi*, compound produced rapid and complete parasite clearance with an ED₅₀ of 0.08 mg/kg i.p. In monkeys infected with *P. falciparum*, complete cure was seen at a dose of 0.2 mg/kg i.m. b.i.d. for 8 days; no recrudescence was found at 60 days, even under conditions of high parasitemia. In rhesus monkeys infected with *Plasmodium cynomolgi*, a twice-daily dose of 0.15 mg/kg i.m. over 8 days cured the animals with no recrudescence at day 36. Compound was not toxic in mice at pharmacological doses (LD₅₀ = 1.4 mg/kg). Studies with a radioactive analogue of compound with potent *in vitro* antimalarial activity (IC₅₀ = 18.3 nM) showed that it specifically accumulated in infected erythrocytes compared to normal red blood cells, and no substantial accumulation was seen in human lymphocytes.

SOURCES – CNRS; Université Montpellier II, Montpellier (FR).

REFERENCES

1. Vial, H. et al. *Antimalarial and anti-babesiosis agents and pharmaceutical compsns. containing same*. FR 2751967, WO 9804252.

2. Calas, M. et al. *Antimalarial activity of compounds interfering with Plasmodium falciparum phospholipid metabolism: Comparison between mono- and bisquaternary ammonium salts*. J Med Chem 2000, 43(3): 505.

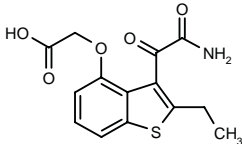
3. Vial, H. et al. *Plasmodium phospholipid metabolism: A target for the development of novel antimalarial drugs*. Ann Trop Med Parasitol 1997, 91(Suppl. 1): S87.

4. Wengelnik, K. et al. *A class of potent antimalarials and their specific accumulation in infected erythrocytes*. Science 2002, 295(5558): 1311.

TREATMENT OF SEPTIC SHOCK

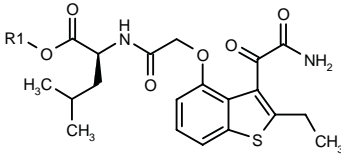
315215

2-[3-(Aminooxalyl)-2-ethyl-1-benzothien-4-yloxy]acetic acid



C14 H13 N O5 S; Mol wt: 307.3247

ACTION – An inhibitor of human nonpancreatic secretory phospholipase A₂ (sPLA₂; IC₅₀ = 1.410 µM against recombinant enzyme), potentially useful for the treatment of inflammatory diseases such as septic shock. Other exemplified compounds are:



Compound	R1	Formula
315216	Me	C ₂₁ H ₂₆ N ₂ O ₆ S
315218	H	C ₂₀ H ₂₄ N ₂ O ₆ S

SOURCE – Lilly.

REFERENCES

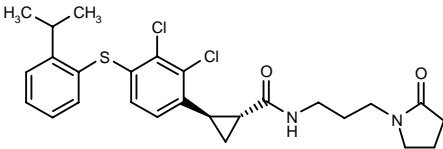
1. Kinnick, M.D. et al. (Eli Lilly and Company) *Novel sPLA 2 inhibitors*. WO 0200641.

TREATMENT OF MUSCULOSKELETAL AND CONNECTIVE TISSUE DISEASES

ANTIARTHRITIC DRUGS

315405

(±)-trans-2-[2,3-Dichloro-4-(2-isopropylphenylsulfanyl)-phenyl]-N-[3-(2-oxopyrrolidin-1-yl)propyl]cyclopropane-carboxamide



C26 H30 Cl2 N2 O2 S; Mol wt: 505.5070

5. Jacobsen, W.M. et al. *Metabolism and adduct formation of K-11777, a novel cysteine protease inhibitor, in vitro (human and rat) and in vivo (rat)*. Annu Meet Am Assoc Pharm Sci (AAPS) (Nov 14-18, New Orleans) 1999, Abst.

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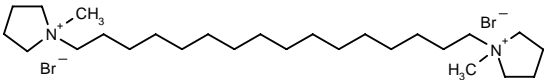
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G25

316877

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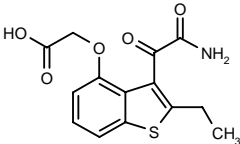
3. Vial, H. et al. *Plasmodium phospholipid metabolism: A target for the development of novel antimalarial drugs*. Ann Trop Med Parasitol 1997, 91(Suppl. 1): S87.

4. Wengelnik, K. et al. *A class of potent antimalarials and their specific accumulation in infected erythrocytes*. Science 2002, 295(5558): 1311.

TREATMENT OF SEPTIC SHOCK

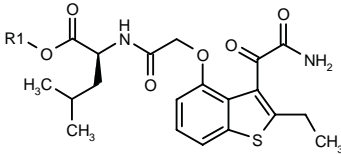
315215

2-[3-(Aminooxalyl)-2-ethyl-1-benzothien-4-yloxy]acetic acid



C14 H13 N O5 S; Mol wt: 307.3247

ACTION – An inhibitor of human nonpancreatic secretory phospholipase A₂ (sPLA₂; IC₅₀ = 1.410 µM against recombinant enzyme), potentially useful for the treatment of inflammatory diseases such as septic shock. Other exemplified compounds are:



Compound	R1	Formula
315216	Me	C ₂₁ H ₂₆ N ₂ O ₆ S
315218	H	C ₂₀ H ₂₄ N ₂ O ₆ S

SOURCE – Lilly.

REFERENCES

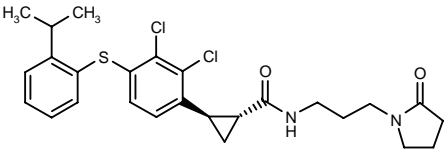
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TREATMENT OF MUSCULOSKELETAL AND CONNECTIVE TISSUE DISEASES

ANTIARTHRITIC DRUGS

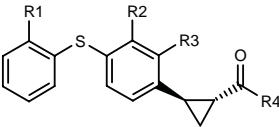
315405

(±)-trans-2-[2,3-Dichloro-4-(2-isopropylphenylsulfanyl)-phenyl]-N-[3-(2-oxopyrrolidin-1-yl)propyl]cyclopropane-carboxamide



C26 H30 Cl2 N2 O2 S; Mol wt: 505.5070

ACTION – Cell adhesion inhibitor that acts by blocking the interaction of the integrin LFA-1 with ICAM-1, ICAM-3 and other adhesion molecules. *In vitro*, it was able to inhibit the interaction of LFA-1 and ICAM-1 by 96% at 2 µM. At the same concentration, compound inhibited the adhesion of JY-8 cells to ICAM-1-coated plates by 92%. Potentially useful as an antiinflammatory and immunosuppressive agent for the treatment of arthritis, asthma, inflammatory lung, liver and glomerular injury, inflammatory bowel disease, type 1 diabetes, radiation-induced enteritis and pneumonitis, reperfusion injury, stroke, peripheral artery occlusion and transplant rejection. Other exemplified compounds are:



Compound	R1	R2	R3	R4	Formula
315406	i-Pr	Cl	Cl	3-CO2H-1-Pip	C ₂₅ H ₂₇ Cl ₂ NO ₃ S
315407	i-Pr	Cl	Cl	NHCH2CH2CO2H	C ₂₂ H ₂₃ Cl ₂ NO ₃ S
315409	i-Pr	Cl	Cl	2-CO2H-1-Pip	C ₂₅ H ₂₇ Cl ₂ NO ₃ S
315410	i-Pr	Cl	Cl	4-morpholinyl	C ₂₃ H ₂₅ Cl ₂ NO ₂ S
315412	3-CO2H-1-Pip	CF3	H	2-oxo-1-pyrrolidinyl-(CH2)3NH	C ₃₀ H ₃₄ F ₃ N ₃ O ₄ S
315413	4-morpholinyl	CF3	H	2-oxo-1-pyrrolidinyl-(CH2)3NH	C ₂₈ H ₃₂ F ₃ N ₃ O ₃ S

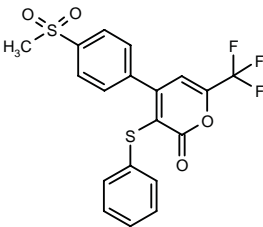
SOURCE – Abbott.

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1. Link, J.T. and Sorensen, B.K. (Abbott Laboratories Inc.) *Aryl phenylcyclopropyl sulfide derivs. and their use as cell adhesion-inhibiting anti-inflammatory and immune-suppressive agents*. WO 0202522.

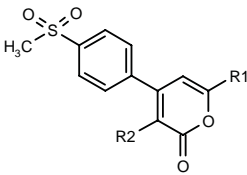
315438

4-[4-(Methylsulfonyl)phenyl]-3-(phenylsulfanyl)-6-(trifluoromethyl)-2H-pyran-2-one



C19 H13 F3 O4 S2; Mol wt: 426.4337

ACTION – A selective inhibitor of cyclooxygenase type 2 (COX-2), giving an IC₅₀ of 0.01 µM against COX-2 expressed in CHO cells, and exhibiting 1,400-fold selectivity over COX-1 expressed in U-937 cells. Potentially useful for the treatment of inflammation, fever and pain associated with a variety of conditions, and also for the treatment of cancer, diabetic retinopathy, dysmenorrhea, preterm labor, asthma, Alzheimer's disease, osteoporosis and glaucoma. Other exemplified 4-phenylpyran-2-one derivatives include the following:



Compound	R1	R2	Formula
315441	H	Ph	C ₁₈ H ₁₄ O ₄ S
315443	Me	4-F-Ph	C ₁₉ H ₁₅ FO ₄ S
315444	Me	3-F-Ph	C ₁₉ H ₁₅ FO ₄ S
315445	Me	Ph	C ₁₉ H ₁₆ O ₄ S
315446	CHF2	Ph	C ₁₉ H ₁₄ F ₂ O ₄ S
315447	CH2F	Ph	C ₁₉ H ₁₅ FO ₄ S
315449	Me	SPh	C ₁₉ H ₁₆ O ₅ S ₂
315451	Me	OPh	C ₁₉ H ₁₆ O ₅ S
315453	Me	3-Pyr	C ₁₈ H ₁₅ NO ₄ S
315456	Me	i-PrS	C ₁₈ H ₁₈ O ₄ S ₂
315458	CF3	i-PrS	C ₁₆ H ₁₅ F ₃ O ₄ S ₂
315460	CH2CF3	Ph	C ₂₀ H ₁₅ F ₃ O ₄ S
315464	Me	CH2CH2C(Me)2OH	C ₁₈ H ₂₂ O ₅ S

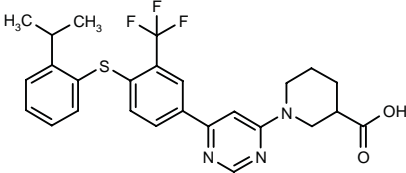
SOURCE – Merck Frosst.

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1. Li, C.-S. et al. (Merck Frosst Canada Inc.) *Pyrones as inhibitors of cyclooxygenase-2*. WO 0202547.

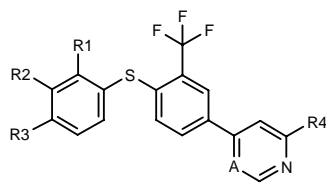
315465

1-[6-[4-(2-Isopropylphenylsulfanyl)-3-(trifluoromethyl)phenyl]pyrimidin-4-yl]piperidine-3-carboxylic acid



C26 H26 F3 N3 O2 S; Mol wt: 501.5704

ACTION – Agent with the ability to inhibit the interaction of the integrin LFA-1 with cell adhesion molecules. Potentially useful for the treatment of acute and chronic inflammation, autoimmune diseases, tumor metastasis, transplant rejection and reperfusion injury. Other specifically claimed phenylsulfanyl derivatives are:



Compound	R1	R2	R3	R4	A	Formula
315467	i-Pr	H	H	3-(2H-5-tetrazolyl)-1-Pip	N	C ₂₆ H ₂₆ F ₃ N ₇ S
315469	i-Pr	H	H	4-(2H-5-tetrazolyl)-1-Pip	N	C ₂₆ H ₂₆ F ₃ N ₇ S
315470	i-Pr	H	H	3-(CH ₂ OH)-1-Pip	N	C ₂₆ H ₂₈ F ₃ N ₃ OS
315471	i-Pr	H	H	4-(CH ₂ CH ₂ OH)-1-Pip	N	C ₂₇ H ₃₀ F ₃ N ₃ OS
315473	i-Pr	H	H	3-(AcNH)-1-pyrrolidinyl	CH	C ₂₇ H ₂₈ F ₃ N ₃ OS
315474	OMe	H	H	3-OH-1-pyrrolidinyl	CH	C ₂₃ H ₂₁ F ₃ N ₂ O ₂ S
315475	OMe	H	H	3-(AcNH)-1-pyrrolidinyl	CH	C ₂₈ H ₂₄ F ₃ N ₃ O ₂ S
315476	H	-OCH ₂ CH ₂ O-		3-(AcNH)-1-pyrrolidinyl	CH	C ₂₆ H ₂₄ F ₃ N ₃ O ₃ S
315478	H	-OCH ₂ CH ₂ O-		4-CO ₂ H-1-Pip	CH	C ₂₆ H ₂₃ F ₃ N ₂ O ₄ S
315479	H	-OCH ₂ CH ₂ O-		3-CO ₂ H-1-Pip	CH	C ₂₆ H ₂₃ F ₃ N ₂ O ₄ S

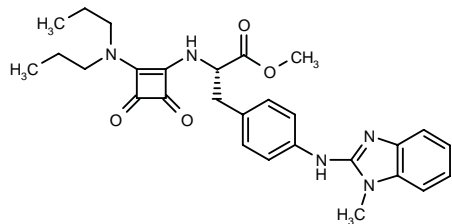
SOURCE – Abbott.

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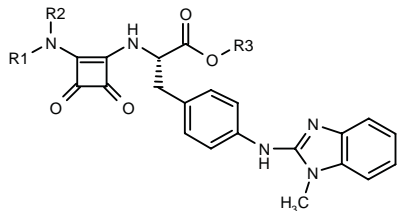
315653

N-[2-(Dipropylamino)-3,4-dioxo-1-cyclobuten-1-yl]-4-(1-methyl-1*H*-benzimidazol-2-ylamino)-L-phenylalanine methyl ester

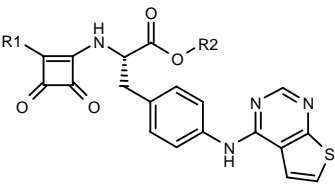


C28 H33 N5 O4; Mol wt: 503.5997

ACTION – A selective inhibitor of α_4 integrins such as $\alpha_4\beta_1$ and $\alpha_4\beta_7$, potentially useful for the treatment of conditions mediated by leukocyte extravasation including rheumatoid arthritis, vasculitis, polydermatomyositis, multiple sclerosis, transplant rejection, diabetes, psoriasis, dermatitis, asthma and inflammatory bowel disease. Other exemplified squaric acid derivatives are:



Compound	R1	R2	R3	Formula
315657	-CH(Me)CH ₂ CH ₂ CH(Me)-		Me	C ₂₈ H ₃₁ N ₅ O ₄
315658	-CH(Me)(CH ₂) ₄ -		Me	C ₂₈ H ₃₁ N ₅ O ₄
315660	Pr	Pr	H	C ₂₇ H ₃₁ N ₅ O ₄
315662	-CH(Me)(CH ₂) ₄ -		H	C ₂₇ H ₂₉ N ₅ O ₄
315784	-CH(Me)CH ₂ CH ₂ CH(Me)-		H	C ₂₇ H ₂₉ N ₅ O ₄



Compound	R1	R2	Formula
315664	i-PrO	Me	C ₂₃ H ₂₂ N ₄ O ₅ S
315666	N(Et) ₂	Et	C ₂₅ H ₂₇ N ₅ O ₄ S
315668	N(Et) ₂	H	C ₂₃ H ₂₃ N ₅ O ₄ S

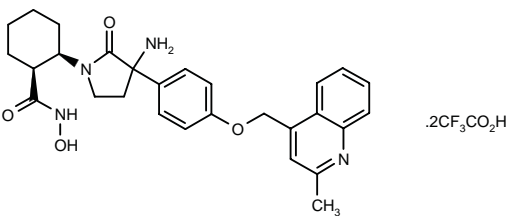
SOURCE – Celltech Group.

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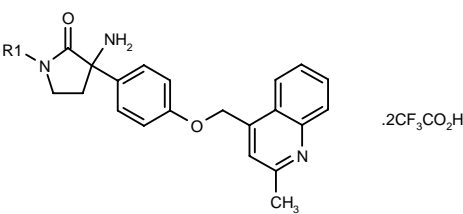
316007

(1*S*,2*R*)-2-[3-Amino-3-[4-(2-methylquinolin-4-ylmethoxy)-phenyl]-2-oxopyrrolidin-1-yl]cyclohexanecarbohydroxamic acid bis(trifluoroacetate)



C28 H32 N4 O4 . 2 C2 H F3 O2; Mol wt: 716.6286

ACTION – Matrix metalloproteinase (MMP) inhibitor for the treatment of inflammatory disorders mediated by MMPs, TNF and/or aggrecanase. Other specifically claimed lactam compounds are:



Compound	R1	Isomer	Formula
316009	(1 <i>R</i> ,2 <i>R</i>)-2-(HONHCO)-cyclohexyl		C ₂₈ H ₃₂ N ₄ O ₄ .2C ₂ HF ₃ O ₂
316010	(1 <i>R</i> ,2 <i>R</i>)-2-CO ₂ H-cyclohexyl		C ₂₈ H ₃₁ N ₃ O ₄ .2C ₂ HF ₃ O ₂
316011	(1 <i>S</i> ,2 <i>R</i>)-2-CO ₂ H-cyclopentyl	S	C ₂₇ H ₂₉ N ₃ O ₄ .2C ₂ HF ₃ O ₂
316012	(1 <i>S</i> ,2 <i>R</i>)-2-(HONHCO)-cyclopentyl	S	C ₂₇ H ₃₀ N ₄ O ₄ .2C ₂ HF ₃ O ₂
316013	(1 <i>R</i> ,2 <i>R</i>)-2-(HONHCO)-cyclopentyl	S	C ₂₇ H ₃₀ N ₄ O ₄ .2C ₂ HF ₃ O ₂
316014	(1 <i>S</i> ,2 <i>R</i>)-2-(HONHCO)-4,4-(Me)2-1-cyclopentyl	S	C ₂₉ H ₃₄ N ₄ O ₄ .2C ₂ HF ₃ O ₂
316015	(1 <i>S</i> ,2 <i>S</i>)-2-(HONHCO)-1-indanyl	S	C ₃₁ H ₃₀ N ₄ O ₄ .2C ₂ HF ₃ O ₂
316016	(3 <i>R</i> ,4 <i>R</i>)-4-(HONHCO)-3-furyl	S	C ₂₆ H ₂₈ N ₄ O ₅ .2C ₂ HF ₃ O ₂
316017	(<i>R</i>)-CH(<i>i</i> -Bu)CH ₂ CONHOH		C ₂₈ H ₃₄ N ₄ O ₄ .2C ₂ HF ₃ O ₂
316018	(<i>R</i>)-CH(<i>i</i> -Bu)CH ₂ CO ₂ H		C ₂₈ H ₃₃ N ₃ O ₄ .2C ₂ HF ₃ O ₂
316019	CH ₂ C(Me) ₂ CONHOH		C ₂₆ H ₃₀ N ₄ O ₄ .2C ₂ HF ₃ O ₂

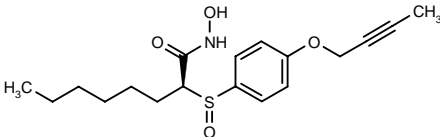
SOURCE – Bristol-Myers Squibb.

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1. Maduskuie, T.P. Jr. et al. (DuPont Pharmaceuticals Co.) *Novel lactam metallo-protease inhibitors*. WO 0204416.

316080

2(S)-[4-(2-Butynyloxy)phenylsulfinyl]octanohydroxamic acid



C18 H25 N O4 S; Mol wt: 351.4645

ACTION – Inhibitor of TNF-α-converting enzyme (TACE) and other matrix metalloproteinases (MMPs), giving IC₅₀ values of 4.3 nM against TACE and of 3 μM, 1500 nM and 900 nM, respectively, against MMP-1 (collagenase 1), MMP-9 (gelatinase B) and MMP-13 (collagenase 3). Potentially useful for the treatment of TNF-α-mediated conditions including rheumatoid arthritis, osteoarthritis, sepsis, AIDS, ulcerative colitis, multiple sclerosis, Crohn’s disease and degenerative cartilage loss.

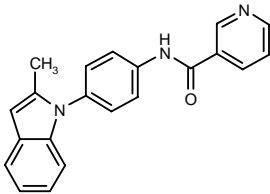
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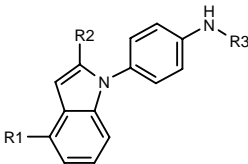
316180

N-[4-(2-Methyl-1 H-indol-1-yl)phenyl]pyridine-3-carboxamide



C21 H17 N3 O; Mol wt: 327.3853

ACTION – Agent with the ability to inhibit the production of IL-2 in T-lymphocytes, potentially useful for the treatment of inflammatory and autoimmune diseases, particularly acute and chronic inflammation, allergies, contact dermatitis, psoriasis, rheumatoid arthritis, multiple sclerosis, type 1 diabetes, inflammatory bowel disease, Guillain-Barré syndrome, Crohn’s disease, ulcerative colitis, transplant rejection and lupus erythematosus. Other exemplified 1-phenylindole derivatives include the following:



Compound	R1	R2	R3	Formula
316185	H	CN	2-Cl-6-Me-PhCH2	C ₂₃ H ₁₈ ClN ₃
316186	Me	SMe	3-Pyr-CO	C ₂₂ H ₁₉ N ₃ OS
316187	4-Pyr	CN	3-Pyr-CO	C ₂₆ H ₁₇ N ₅ O
316190	2-THF	CN	3-Pyr-CO	C ₂₅ H ₂₀ N ₄ O ₂
316191	3-furyl	Me	3-Pyr-CO	C ₂₅ H ₁₉ N ₃ O ₂
316193	2-thiazolyl	Me	3-Pyr-CO	C ₂₄ H ₁₈ N ₄ OS
316195	2-thiazolyl	SMe	3-Pyr-CO	C ₂₄ H ₁₈ N ₄ OS ₂

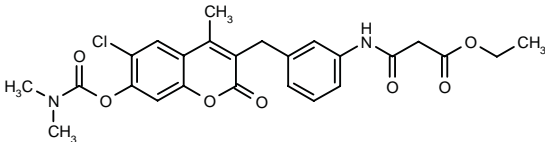
SOURCE – Boehringer Ingelheim.

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1. Sharma, R. (Boehringer Ingelheim Pharmaceuticals Inc.) *Substd. 1-(4-amino-phenyl)indoles and their use as anti-inflammatory agents*. US 6353007, WO 0206273.

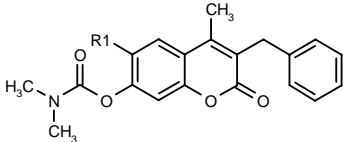
316472

N-[3-[6-Chloro-7-(dimethylaminocarbonyloxy)-4-methyl-2-oxo-2H-1-benzopyran-3-ylmethyl]phenyl]malonamic acid ethyl ester



C25 H25 Cl N2 O7; Mol wt: 500.9325

ACTION – TNF-α production inhibitor, as demonstrated in human peripheral blood mononuclear cells (IC₅₀ = 0.05 μM). Potentially useful for the treatment of immuno-inflammatory disorders, particularly autoimmune diseases. Other exemplified coumarin derivatives are:



Compound	R1	Formula
316473	I	C ₂₀ H ₁₈ INO ₄
316474	Br	C ₂₀ H ₁₈ BrNO ₄
316475	Cl	C ₂₀ H ₁₈ ClNO ₄

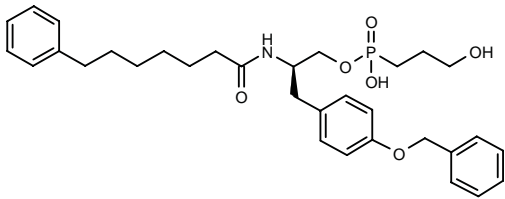
SOURCE – Chugai.

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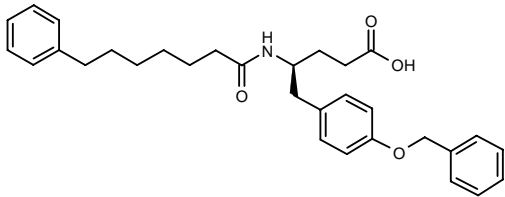
316658

3-Hydroxypropylphosphonic acid 3-[4-(benzyloxy)phenyl]-2(*R*)-(7-phenylheptanamido)propyl ester



C32 H42 N O6 P; Mol wt: 567.6588

ACTION – An inhibitor of nonpancreatic secretory phospholipase A₂ (sPLA₂; IC₅₀ = 24 nM), potentially useful for the treatment of inflammatory diseases including rheumatoid arthritis, multiple sclerosis, osteoarthritis, psoriasis, surgical adhesions, Crohn’s disease, dermatitis, ulcers, lupus, immune diseases, cystic fibrosis, atherosclerosis, fibrosis, hypotension, asthma, allergy, reperfusion injury, myocardial infarction, ischemia, Alzheimer’s disease, dysmenorrhea, type 1 diabetes, pancreatitis, pulmonary diseases, malaria, dermatitis, adult respiratory distress syndrome, sepsis, uveitis, vascular diseases, synovitis, peritonitis, cancer, meningitis, retinitis and transplant rejection. Another exemplified compound is:



316659: C31 H37 N O4

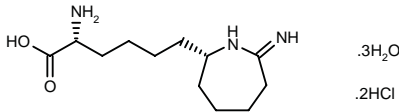
SOURCE – University of Queensland, Queensland (AU).

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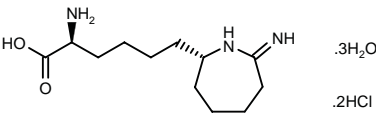
316802

2(*R*)-Amino-6-[7-iminoperhydroazepin-2(*S*)-yl]hexanoic acid dihydrochloride trihydrate



C12 H23 N3 O2 . 2HCl . 3H2O; Mol wt: 368.2989

ACTION – A selective inhibitor of inducible nitric oxide synthase (iNOS) giving IC₅₀ values of < 3, > 30 and > 3 μM, respectively, against iNOS, endothelial NOS (eNOS) and neuronal NOS (nNOS); it inhibited lipopolysaccharide S (LPS)-induced nitrite production in human cartilage cells with an IC₅₀ < 10 μM. *In vivo*, compound was able to inhibit the LPS-induced increase in nitrite/nitrate plasma levels when orally administered to rats (ED₅₀ < 3 mg/kg). Potentially useful for the treatment of pain, migraine, arthritis, asthma, bronchitis, dysmenorrhea, preterm labor, psoriasis, dermatitis, pancreatitis, hepatitis, inflammatory bowel disease, Crohn’s disease, gastritis, ulcerative colitis, inflammation, ophthalmic diseases such as glaucoma, pulmonary inflammation, Alzheimer’s disease, atherosclerosis, rhinitis, etc. Another exemplified compound is:



316803: C12 H23 N3 O2 . 2HCl . 3H2O

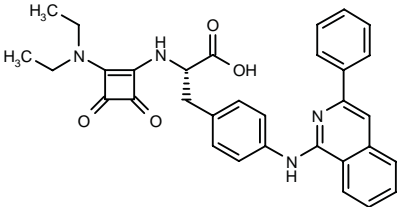
SOURCE – Pharmacia.

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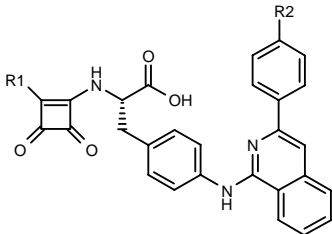
316859

N-[2-(Diethylamino)-3,4-dioxo-1-cyclobuten-1-yl]-4-(3-phenylisoquinolin-1-ylamino)-L-phenylalanine



C32 H30 N4 O4; Mol wt: 534.6130

ACTION – Potent and selective inhibitor of α₄β₁ and/or α₄β₇ integrins, potentially useful for the treatment of immune and inflammatory disorders such as arthritis, multiple sclerosis, transplant rejection, diabetes, psoriasis, dermatitis, asthma and inflammatory bowel disease, among others. Other specifically claimed isoquinoline derivatives are:



Compound	R1	R2	Formula
316860	2,5-(Me)2-1-pyrrolidiny	H	C ₃₄ H ₃₂ N ₄ O ₄
316861	2,5-(Me)2-1-pyrrolidiny	F	C ₃₄ H ₃₁ FN ₄ O ₄
316867	i-PrN(Et)	H	C ₃₃ H ₃₂ N ₄ O ₄
316868	hexahydro-1-azepiny	H	C ₃₄ H ₃₂ N ₄ O ₄

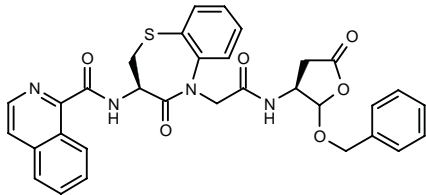
SOURCE – Celltech Group.

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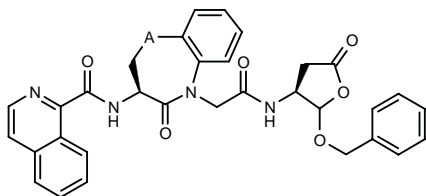
317442

N-[5-[*N*-[2-(Benzyloxy)-5-oxotetrahydrofuran-3(*S*)-yl]carbamoylmethyl]-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3(*R*)-yl]isoquinoline-1-carboxamide



C32 H28 N4 O6 S; Mol wt: 596.6612

ACTION – IL-1 β -converting enzyme (ICE) inhibitor shown to inhibit IL-1 β production in lipopolysaccharide (LPS)-challenged mice by 74% at 100 mg/kg p.o. Potentially useful for the treatment of disorders mediated by IL-1 such as inflammatory, autoimmune, proliferative, infectious and degenerative diseases, as well as destructive bone disorders. In particular, compound is expected to be useful for the treatment of osteoarthritis, rheumatoid arthritis, psoriasis, glomerulonephritis, transplant rejection and sepsis. Other exemplified compounds are:



Compound	A	Formula
317444	-O-	C ₃₂ H ₂₈ N ₄ O ₇
317445	-CO-	C ₃₃ H ₂₈ N ₄ O ₇

SOURCE – Vertex.

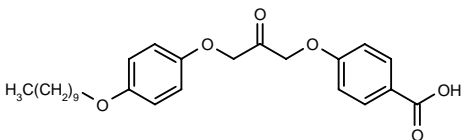
REFERENCES

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AR-C70484XX

316754

4-[3-[4-(Decyloxy)phenoxy]-2-oxopropoxy]benzoic acid



C26 H34 O6; Mol wt: 442.5486

ACTION – Cytosolic phospholipase A₂ (cPLA₂) inhibitor (IC₅₀ = 8 and 30 nM for inhibition of cPLA₂ in a bilayer assay and a soluble substrate assay, respectively) that is also able to inhibit the production of arachidonic acid in HL-60 cells (IC₅₀ = 2.8 μ M) with higher potency than the standard cPLA₂ inhibitor arachidonyl trifluoromethyl ketone (IC₅₀ = 29 μ M). Potentially useful as an antiinflammatory agent.

SOURCE – AstraZeneca.

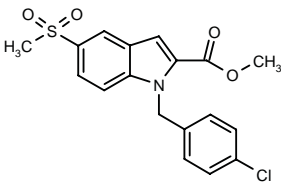
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LM-1685

317421

1-(4-Chlorobenzyl)-5-(methylsulfonyl)-1*H*-indole-2-carboxylic acid methyl ester



C18 H16 Cl N O4 S; Mol wt: 377.8464

ACTION – Potent and selective cyclooxygenase type 2 (COX-2) inhibitor (IC₅₀ = 0.65 and 4.3 μ M in PGE₂ and human whole blood assay, respectively) with more than 20-fold selectivity over the COX-1 isoform. Compared with celecoxib and rofecoxib, compound exhibited comparable COX-2-inhibitory activity but more favorable selectivity over COX-1. Potentially useful as an antiinflammatory agent.

SOURCE – Menarini.

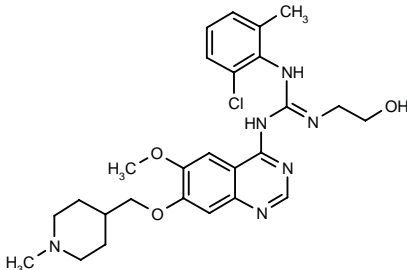
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1. Palomer, A. et al. *Identification of novel cyclooxygenase-2 selective inhibitors using pharmacophore models.* J Med Chem 2002, 45(7): 1402.

IMMUNOMODULATING AGENTS

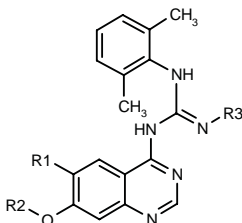
315073

N-(2-Chloro-6-methylphenyl)-*N*'-(2-hydroxyethyl)-*N*''-[6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazolin-4-yl]guanidine



C26 H33 Cl N6 O3; Mol wt: 513.0387

ACTION – Immunosuppressant with potential in the treatment of T-cell-mediated disorders, particularly transplant rejection and rheumatoid arthritis. Other exemplified compounds within this series of quinazoline and quinoline derivatives are:



Compound	R1	R2	R3	Formula
315075	OMe	1-Me-4-Pip-CH2	CH2CO2H	C ₂₇ H ₃₄ N ₆ O ₄
315077	OMe	1-Me-4-Pip-CH2	CH2CH2NH2	C ₂₇ H ₃₇ N ₇ O ₂
315079	OMe	4-morpholinyl-(CH2)3	CH2CH2C(=NH)NH2	C ₂₈ H ₃₈ N ₆ O ₃
315081	OMe	H	CH2CH2N(Me)2	C ₂₂ H ₂₈ N ₆ O ₂
315082	OMe	1-Me-3-pyrrolidinyl	(CH2)3N(Me)2	C ₂₈ H ₃₉ N ₇ O ₂
315084	OMe	1-pyrrolidinyl-CH2CH2	(S)-CH(Me)CO2H	C ₂₇ H ₃₄ N ₆ O ₄
315085	OMe	3-morpholinyl-CH2	CH2CH2N(Me)2	C ₂₇ H ₃₇ N ₇ O ₃
315086	H	4-morpholinyl-CH2CH2	CH2CH2CN	C ₂₆ H ₃₁ N ₇ O ₂

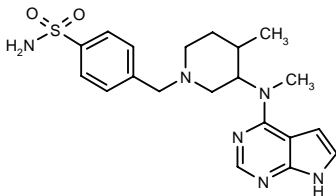
SOURCE – AstraZeneca.

REFERENCES

1. Poyser, J.P. (AstraZeneca AB;AstraZeneca plc) *Guanidine derivs. of quinazoline and quinoline for use in the treatment of autoimmune diseases*. WO 0200644.

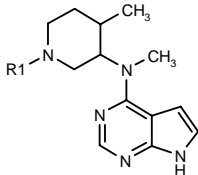
315225

4-[4-Methyl-3-[*N*-methyl-*N*-(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]piperidin-1-ylmethyl]benzenesulfonamide



C20 H26 N6 O2 S; Mol wt: 414.5314

ACTION – Immunosuppressant, an inhibitor of Janus kinase 3 (JAK3), potentially useful for the treatment of transplant rejection, lupus, multiple sclerosis, rheumatoid arthritis, psoriasis, type 1 diabetes and complications related therewith, cancer, asthma, atopic dermatitis, autoimmune thyroid disorders, ulcerative colitis, Crohn's disease, Alzheimer's disease and leukemia. Other exemplified pyrrolo[2,3-*d*]pyrimidine derivatives include the following:



Compound	R1	Formula
315236	1-tetrazolyl-CH2CO	C ₁₆ H ₂₁ N ₉ O
315248	5-NO2-2-Pyr	C ₁₈ H ₂₁ N ₇ O ₂
315265	4-(EtOCOCH2)-2-thiazolyl-NHCO	C ₂₁ H ₂₇ N ₇ O ₃ S
315274	1-pyrrolidinyl-CO	C ₁₈ H ₂₆ N ₆ O
315276	6-CN-3-Pyr-NHCO	C ₂₀ H ₂₂ N ₈ O
315277	cyclopentyl-CO	C ₁₉ H ₂₇ N ₅ O
315278	3-Me-5-isothiazolyl-NHCO	C ₁₈ H ₂₃ N ₇ OS

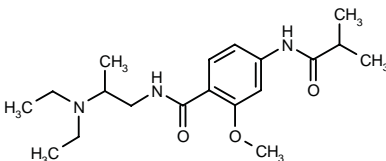
SOURCE – Pfizer.

REFERENCES

1. Blumenkopf, T.A. et al. (Pfizer Products Inc.) *Pyrrolo[2,3-d]pyrimidine cpds. as immunosuppressive agents*. WO 0200661.

315363

N-[2-(Diethylamino)propyl]-4-isobutyramido-2-methoxybenzamide



C19 H31 N3 O3; Mol wt: 349.4719

ACTION – A representative compound from a group of *N*-substituted benzamides with the ability to enhance transcription factor activator protein-1 (AP-1). By virtue of its immunostimulant activity, compound is expected to be useful for the treatment of cancer, cytostatic- and radiation-related immunosuppression, autoimmune diseases and infectious diseases. Since AP-1 plays a role in manic depressive illness, it is also potentially useful for the treatment of bipolar disorder.

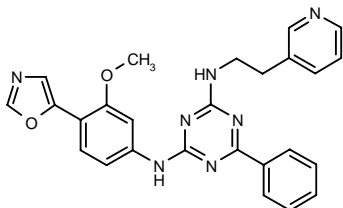
SOURCE – Active Biotech.

REFERENCES

1. Björk, A. et al. (Active Biotech AB) *Substd. benzamides for immune enhancement and for the treatment of cancer, infection and manic-depressive illness*. WO 0202511.

318212

*N*²-[3-Methoxy-4-(5-oxazolyl)phenyl]-6-phenyl-*N*⁴-[2-(3-pyridyl)ethyl]-1,3,5-triazine-2,4-diamine



C₂₆ H₂₃ N₇ O₂; Mol wt: 465.5147

ACTION – Potential immunosuppressant, an inhibitor of IMP dehydrogenase (IC₅₀ = 54 nM) that selectively inhibits the proliferation of T-cells (IC₅₀ = 2.3 μM) with no cytotoxicity against other cells.

SOURCE – Bristol-Myers Squibb.

REFERENCES

1. Liu, C. et al. (Bristol-Myers Squibb Co.) *Cpds. derived from an amine nucleus that are inhibitors of IMPDH enzyme*. EP 1126843, WO 0025780.
2. Guo, J. et al. *Rapid synthesis of novel inosine monophosphate dehydrogenase (IMPDH) inhibitors*. 223rd ACS Natl Meet (April 7-11, Orlando) 2002, Abst MEDI 214.

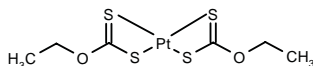
ONCOLYTIC DRUGS

DNA-DAMAGING DRUGS

THIOPLATIN

295490

(*SP*-4-1)-Bis(*O*-ethyl carbonodithioato-κS,κS')platinum



C₆ H₁₀ O₂ Pt S₄; Mol wt: 437.4870

ACTION – Cisplatin analogue, a sulfur-containing platinum complex that, unlike cisplatin, was more potent against a range of cells at the more acidic pH found in solid tumors than at pH levels found in normal tissues. Compound was active *in vitro* against the NCI 60 human tumor cell line panel, with a mean GI₅₀ value of 12.5 μM, including ovarian cancer cell lines with acquired resistance to cisplatin and cell lines overexpressing the multidrug resistance P-glycoprotein efflux pump. In studies in mice bearing human small cell lung carcinoma H10 cells or cisplatin-resistant human colorectal carcinoma SW707 cells, compound showed comparable activity to cisplatin but a 5-10-fold higher therapeutic index.

SOURCES – Antisoma; Deutsches Krebsforschungszentrum, Heidelberg (DE).

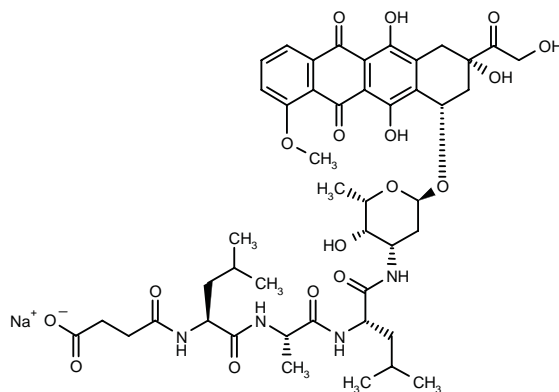
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2. Amtmann, E. et al. *Antitumoral activity of a sulphur-containing platinum complex with an acidic pH optimum*. Cancer Chemother Pharmacol 2001, 47(6): 461.
3. Rowlinson-Busza, G. et al. *Thioplantin: A sulfur-containing platinum complex possessing greater activity in acidic pH, non-cross resistance with cisplatin and antitumor activity in vivo*. Proc Amer Assoc Cancer Res 2002, 43: Abst 309.
4. *Antisoma enters supply agreement for thioplantin*. DailyDrugNews.com (Daily Essentials) 2001, July 17.
5. *Antisoma highlights recent product developments*. DailyDrugNews.com (Daily Essentials) 2001, Feb 26.
6. *Antisoma licenses thioplantin from German cancer center*. DailyDrugNews.com (Daily Essentials) 2000, Oct 30.
7. *Antisoma sees further progress on all fronts during the first quarter*. DailyDrugNews.com (Daily Essentials) 2001, Nov 12.

ANTIBIOTICS AND ALKALOIDS

315275

N-[*N*-(4-Hydroxysuccinyl)-L-leucyl-L-alanyl-L-leucyl]doxorubicin sodium salt

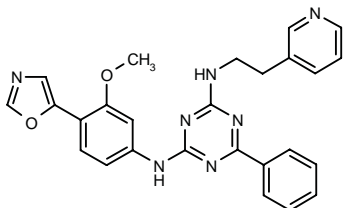


C₄₆ H₅₉ N₄ Na O₁₇; Mol wt: 962.9731

ACTION – Tripeptide prodrug of doxorubicin with an improved toxicity profile, potentially useful for the treatment of cancer, inflammatory diseases and infections. This prodrug was shown to be cleaved to doxorubicin when treated with HeLa cell trouase, and gave IC₅₀ values of 1.0, 36 and 50 μM, respectively, against human prostate LNCaP, human colon adenocarcinoma HT-29 and human prostate adenocarcinoma PC-3 tumor cell lines. It demonstrated a better safety profile than doxorubicin when given i.v. to both tumor-free and tumor-bearing mice, and presented appropriate pharmacokinetic behavior, since it was rapidly cleared from the circulation to be excreted mainly via the urine. The prodrug was shown to be more effective than doxorubicin when administered to mice bearing human colon carcinoma LS 174T xenografts.

318212

*N*²-[3-Methoxy-4-(5-oxazolyl)phenyl]-6-phenyl-*N*⁴-[2-(3-pyridyl)ethyl]-1,3,5-triazine-2,4-diamine



C₂₆ H₂₃ N₇ O₂; Mol wt: 465.5147

ACTION – Potential immunosuppressant, an inhibitor of IMP dehydrogenase (IC₅₀ = 54 nM) that selectively inhibits the proliferation of T-cells (IC₅₀ = 2.3 μM) with no cytotoxicity against other cells.

SOURCE – Bristol-Myers Squibb.

REFERENCES

1. Liu, C. et al. (Bristol-Myers Squibb Co.) *Cpds. derived from an amine nucleus that are inhibitors of IMPDH enzyme*. EP 1126843, WO 0025780.
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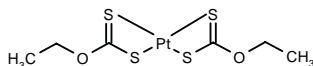
ONCOLYTIC DRUGS

DNA-DAMAGING DRUGS

THIOPLATIN

295490

(*SP*-4-1)-Bis(*O*-ethyl carbonodithioato-κS,κS')platinum



C₆ H₁₀ O₂ Pt S₄; Mol wt: 437.4870

ACTION – Cisplatin analogue, a sulfur-containing platinum complex that, unlike cisplatin, was more potent against a range of cells at the more acidic pH found in solid tumors than at pH levels found in normal tissues. Compound was active *in vitro* against the NCI 60 human tumor cell line panel, with a mean GI₅₀ value of 12.5 μM, including ovarian cancer cell lines with acquired resistance to cisplatin and cell lines overexpressing the multidrug resistance P-glycoprotein efflux pump. In studies in mice bearing human small cell lung carcinoma H10 cells or cisplatin-resistant human colorectal carcinoma SW707 cells, compound showed comparable activity to cisplatin but a 5-10-fold higher therapeutic index.

SOURCES – Antisoma; Deutsches Krebsforschungszentrum, Heidelberg (DE).

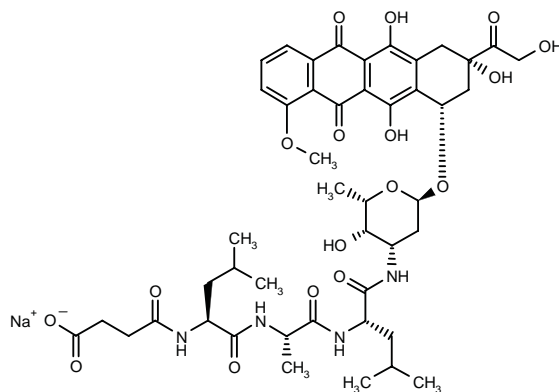
REFERENCES

1. Amtmann, E. and Schilling, G. (Deutsches Krebsforschungszentrum; Ruprecht-Karls-Universität Heidelberg) *Medicament containing platinum complex cpds. and the use thereof*. WO 0010543.
2. Amtmann, E. et al. *Antitumoral activity of a sulphur-containing platinum complex with an acidic pH optimum*. Cancer Chemother Pharmacol 2001, 47(6): 461.
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5. *Antisoma highlights recent product developments*. DailyDrugNews.com (Daily Essentials) 2001, Feb 26.
6. *Antisoma licenses thioplantin from German cancer center*. DailyDrugNews.com (Daily Essentials) 2000, Oct 30.
7. *Antisoma sees further progress on all fronts during the first quarter*. DailyDrugNews.com (Daily Essentials) 2001, Nov 12.

ANTIBIOTICS AND ALKALOIDS

315275

N-[*N*-(4-Hydroxysuccinyl)-L-leucyl-L-alanyl-L-leucyl]doxorubicin sodium salt



C₄₆ H₅₉ N₄ Na O₁₇; Mol wt: 962.9731

ACTION – Tripeptide prodrug of doxorubicin with an improved toxicity profile, potentially useful for the treatment of cancer, inflammatory diseases and infections. This prodrug was shown to be cleaved to doxorubicin when treated with HeLa cell trouase, and gave IC₅₀ values of 1.0, 36 and 50 μM, respectively, against human prostate LNCaP, human colon adenocarcinoma HT-29 and human prostate adenocarcinoma PC-3 tumor cell lines. It demonstrated a better safety profile than doxorubicin when given i.v. to both tumor-free and tumor-bearing mice, and presented appropriate pharmacokinetic behavior, since it was rapidly cleared from the circulation to be excreted mainly via the urine. The prodrug was shown to be more effective than doxorubicin when administered to mice bearing human colon carcinoma LS 174T xenografts.

SOURCE – Corixa.

REFERENCES

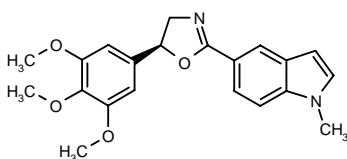
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ANTIMITOTIC DRUGS

A-289099

317844

1-Methyl-5-[5(*S*)-(3,4,5-trimethoxyphenyl)-4,5-dihydro-oxazol-2-yl]-1*H*-indole



C21 H22 N2 O4; Mol wt: 366.4148

ACTION – Orally active antimitotic agent proven to inhibit bovine brain tubulin polymerization with an IC_{50} of 2.3 μ M by binding to the colchicine site ($K_i = 0.63 \mu$ M). Compound induced accumulation of cells in the G_2/M phase, followed by the induction of apoptosis; it showed antiproliferative activity against human non-small cell lung carcinoma NCI-H460 cells expressing low levels of P-glycoprotein ($IC_{50} = 6.2$ nM) and multidrug-resistant (MDR) human colon adenocarcinoma HCT-15 cells expressing high levels of P-glycoprotein ($IC_{50} = 8.6$ nM). Pharmacokinetic studies in mice, rats, dogs and monkeys demonstrated respective oral bioavailabilities of 15.1, 17.1, 6.5 and 18.6%. In mice bearing murine ovarian sarcoma M5076, compound given orally at the maximum tolerated dose of 100 mg/kg/day for 28 days significantly increased life span (ILS = 206%) and induced a 28-day mean tumor growth delay; an increase in apoptosis and antivascular effects were also seen.

SOURCE – Abbott.

REFERENCES

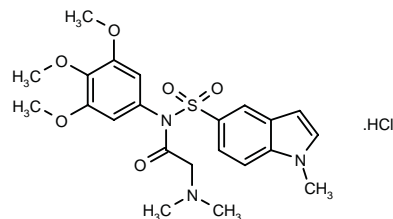
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A-318315

317845

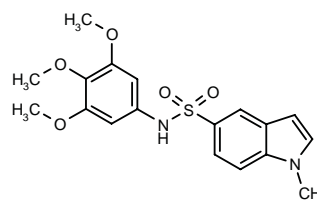
N-[2-(Dimethylamino)acetyl]-1-methyl-*N*-(3,4,5-trimethoxyphenyl)-1*H*-indole-5-sulfonamide hydrochloride

*N*²,*N*²-Dimethyl-*N*¹-(1-methyl-1*H*-indol-5-ylsulfonyl)-*N*¹-(3,4,5-trimethoxyphenyl)glycinamide hydrochloride



C22 H27 N3 O6 S . HCl; Mol wt: 497.9972

ACTION – Dimethylglycine prodrug of the antimitotic agent **A-293620**, which inhibits tubulin polymerization by binding to the colchicine site and shows strong activity against a broad spectrum of tumor cell lines including multidrug-resistant (MDR) lines ($IC_{50} = 12.42$ nM). The prodrug displayed an improved solubility and pharmacokinetic profile and good oral activity in several animal tumor models. In the syngeneic mouse reticulosarcoma M5076 model, oral doses of 56, 75 or 100 mg/kg/day p.o. for 5 days significantly inhibited tumor growth, with respective T/C values of 81, 56 and 24%; mice were tumor-free following treatment for 21 days at doses of 100 and 133 mg/kg/day. Compound also significantly inhibited the growth of human colon adenocarcinoma HCT-15 xenografts expressing high levels of P-glycoprotein following daily oral administration at doses of 75-133 mg/kg/day for 8 days; in this model, paclitaxel and vincristine were inactive. In addition, compound induced tumor-selective antivascular effects and promoted apoptosis after single i.v. or i.p. doses in the rat glioma 9L tumor model.



A-293620 [298291]: C18 H20 N2 O5 S

SOURCE – Abbott.

REFERENCES

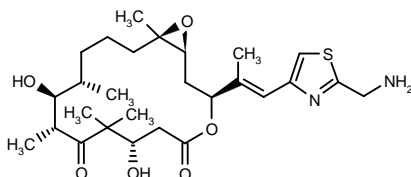
1. Qun, L. et al. (Abbott Laboratories Inc.) *Cell proliferation inhibitors.* WO 0073264.
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3. Zielinski Mozny, N. et al. *Biological efficacy of A-318315, an orally active antimitotic agent.* Proc Amer Assoc Cancer Res 2002, 43: Abst 1314.

BMS-310705*

294121

[1*S*,3*S*(*E*),7*S*,10*R*,11*S*,12*S*,16*R*]-3-[2-[2-(Aminomethyl)-thiazol-4-yl]-1-methylvinyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione

21-Aminoepothilone B



C27 H42 N2 O6 S; Mol wt: 522.7028

ACTION – Epothilone derivative, a water-soluble and chemically stable compound shown to be more effective than paclitaxel or epothilone B or D in taxane-sensitive and -resistant human tumor xenograft models in mice. In platinum- and paclitaxel-refractory ovarian cancer cells, compound (0.05-1 μ M) induced apoptosis, an effect which appeared to be mediated by early activation of caspases 9 and 6, followed later by activation of caspases 2 and 3, but which did not appear to involve an NF- κ B-dependent pathway. Compound was orally active and exhibited a toxicity profile similar to paclitaxel. Phase I trials are in progress.

SOURCES – Bristol-Myers Squibb; GBF.

REFERENCES

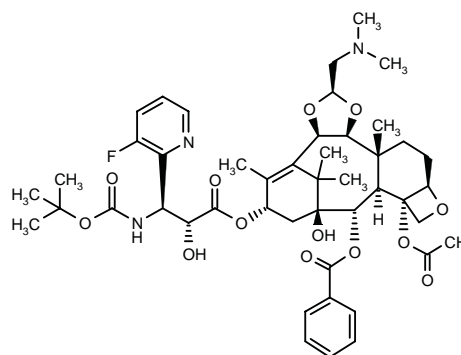
1. Hoefle, G. et al. (Gesellschaft für Biotechnologische Forschung mbH; Bristol-Myers Squibb Co.) *C-21 modified epothilones*. DE 19907588, EP 1157023, US 6262094, WO 0050423.
2. Lee, F.Y. (Bristol-Myers Squibb Co.) *Synergistic methods and compsns. for treating cancer*. WO 0172721.
3. Lee, F.Y. et al. *The discovery of BMS-310705: A water-soluble and chemically stable semi-synthetic epothilone possessing potent parenteral and oral antitumor activity against models of taxane-sensitive and -resistant human tumors in vivo*. Proc Amer Assoc Cancer Res 2002, 43: Abst 3928.
4. Uyar, D. et al. *Characterization of cell death mechanisms of BMS-310705, an epothilone derivative*. Proc Amer Assoc Cancer Res 2002, 43: Abst 4571.
5. Vite, G. et al. *The semisynthesis and preclinical evaluation of BMS-310705, an epothilone analog in clinical development*. 223rd ACS Natl Meet (April 7-11, Orlando) 2002, Abst MEDI 18.

*Identified compound **294121** (see **294110**) Drug Data Rep 2001, 023(02): 0178.

DJ-927*

304277

Benzoic acid (2*aS*,2*bR*,3*S*,4*S*,6*S*,8*aR*,10*S*,11*aS*,11*bR*,13*aR*)-2*a*-acetoxy-6-[3(*S*)-(tert-butoxycarboxamido)-3-(3-fluoropyridin-2-yl)-2(*R*)-hydroxypropanoyloxy]-10-(dimethylaminomethyl)-4-hydroxy-7,11*b*,14,14-tetramethyl-2*a*,2*b*,3,4,5,6,8*a*,11*a*,11*b*,12,13,13*a*-dodecahydro-4,8-methano-2*H*-oxeto[3'',2'':3',4']benzo[1',2':3,4]-cyclodeca[1,2-*d*][1,3]dioxol-3-yl ester



C46 H60 F N3 O13; Mol wt: 881.9860

ACTION – Orally active taxane proven to be 3-10-fold more active than paclitaxel and docetaxel against 10 sensitive and resistant human tumor cell lines (GI_{50} = 0.2-1.3, 0.6-60 and 0.2-13 ng/ml, respectively). Experiments with [14 C]-labeled compound indicated that its stronger activity against MDR tumor cells is due to higher intracellular accumulation. Orally administered DJ-927 exerted superior *in vivo* antitumor activity compared to i.v. paclitaxel and docetaxel against several human tumor xenografts in athymic mice including P-glycoprotein-positive colon cancer DLD-1 and breast cancer DU4475 xenografts. Compound showed a better safety profile compared to the other taxanes; the major toxicity consisted of myelosuppression and gastrointestinal disturbances, but no peripheral neuropathy or clinical signs were seen in mice. Pharmacokinetic studies in mice, dogs and monkeys showed rapid oral absorption with peak plasma levels reached within 1-2 h; elimination was biphasic and the half-life was much longer in dogs ($t_{1/2}$ = 4 days) than in monkeys or mice ($t_{1/2}$ = 1.2-2.2 days). The bioavailability was 50-100% in these species.

SOURCE – Daiichi Pharmaceutical.

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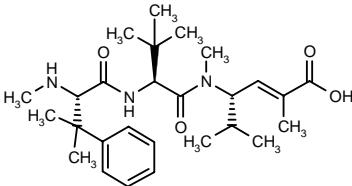
*Identified compound **304277** Drug Data Rep 2001, 023(09): 0918.

HTI-286

317936

N,3,3-Trimethyl-L-phenylalanyl-*N*¹-[3-carboxy-1(*S*)-isopropyl-2-butenyl]-*N*¹,3-dimethyl-L-valinamide

SPA-110 (as trifluoroacetate salt)



C27 H43 N3 O4; Mol wt: 473.6537

ACTION – Antineoplastic agent, a synthetic derivative of the natural peptide hemiasterlin, proven to inhibit polymerization of purified tubulin in cell-free assays and depolymerize cellular microtubules and thereby produce cell cycle arrest and apoptosis. Compound strongly inhibited the proliferation of a range of tumor cells with a mean IC₅₀ of 2.5 nM, and it was active against tumor cell lines overexpressing the ABCB1, ABCC1 and ABCG2 drug transporters, as well as tumor cells with tubulin mutations conferring paclitaxel or epothilone resistance. Compound was active after i.v. or oral administration in various human tumor xenograft models including tumors resistant to paclitaxel and vincristine. Currently undergoing clinical evaluation.

SOURCES – University of British Columbia, Vancouver, BC (CA); Wyeth Research.

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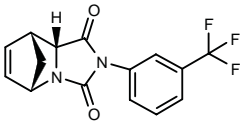
2. Loganzo, F. et al. *HTI-286, a synthetic analog of the anti-microtubule tripeptide hemiasterlin, potently inhibits growth of cultured tumor cells, overcomes resistance to paclitaxel mediated by various mechanisms, and demonstrates intravenous and oral in vivo efficacy.* Proc Amer Assoc Cancer Res 2002, 43: Abst 1316.

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HORMONAL AGENTS

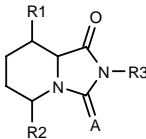
315223

(5α,8α,8aα)-2-[3-(Trifluoromethyl)phenyl]-1,2,3,5,8,8a-hexahydro-5,8-methanoimidazo[1,5-*a*]pyridine-1,3-dione

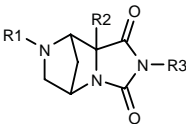


C15 H11 F3 N2 O2; Mol wt: 308.2579

ACTION – Agent with the ability to modulate nuclear hormone receptors, potentially useful for the treatment of conditions mediated by estrogen, progesterone, glucocorticoid, mineralocorticoid, aldosterone and androgen receptors. Examples of these conditions are cancer, benign prostatic hypertrophy, heart disease, angiogenesis, hirsutism, acne, inflammation, immune disorders, endometriosis, polycystic ovary syndrome, alopecia, hypogonadism, osteoporosis, cachexia, anorexia, hot flushes, menopause, amenorrhea, dysmenorrhea, endometriosis, Alzheimer's disease, drug abuse, psychosis and type 2 diabetes. Other exemplified fused cyclic compounds are:



Compound	R1,R2	R3	A	Isomer	Formula
315226	-CH2-	2-Naph	-N(Ph)-	5α,8α,8aα	C ₂₄ H ₂₁ N ₃ O
315228	-CH2-	3,5-(Cl)2-Ph	-O-	5R,8S,8aS	C ₁₄ H ₁₂ Cl ₂ N ₂ O ₂
315229	-CH2-	3-Cl-4-F-Ph	-N(CN)-	5α,8α,8aα	C ₁₅ H ₁₂ ClFN ₄ O
315230	-CH2-	3-CF3-4-CN-Ph	-O-	5α,8α,8aα	C ₁₆ H ₁₂ F ₃ N ₃ O ₂
315231	-(CH2)2-	1-Naph	-O-		C ₁₉ H ₁₈ N ₂ O ₂



Compound	R1	R2	R3	Isomer	Formula
315232	H	H	3-CF3-4-CN-Ph	5S,8S,8aR	C ₁₅ H ₁₁ F ₃ N ₄ O ₂
315233	COPh	Me	3-CF3-4-CN-Ph	5S,8S,8aR	C ₂₃ H ₁₇ F ₃ N ₄ O ₃
315235	CH2Ph	H	4-NO2-1-Naph	5S,8S,8aS	C ₂₄ H ₂₀ N ₄ O ₄

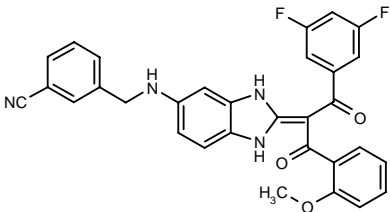
SOURCE – Bristol-Myers Squibb.

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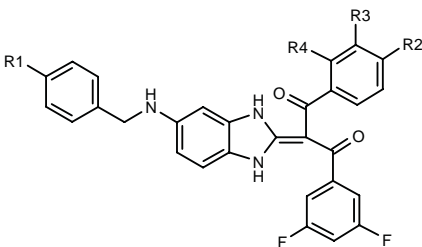
315491

3-[2-[1-(3,5-Difluorobenzoyl)-2-(2-methoxyphenyl)-2-oxo-ethylidene]-2,3-dihydro-1*H*-benzimidazol-5-ylamino-methyl]benzonitrile



C31 H22 F2 N4 O3; Mol wt: 536.5358

ACTION – Gonadotropin-releasing hormone (GnRH) antagonist for the treatment of sex hormone-related diseases including prostate cancer, breast cancer, endometriosis and uterine myoma. Other exemplified propane-1,3-dione derivatives are:



Compound	R1	R2	R3	R4	Formula
315494	i-PrNHCO	H	H	H	C ₃₃ H ₂₈ F ₂ N ₄ O ₃
315495	NHAc	H	H	Me	C ₃₂ H ₂₆ F ₂ N ₄ O ₃
315496	NHAc	H	OCF ₃	H	C ₃₂ H ₂₃ F ₅ N ₄ O ₄
315497	NHAc	OMe	H	H	C ₃₂ H ₂₆ F ₂ N ₄ O ₄

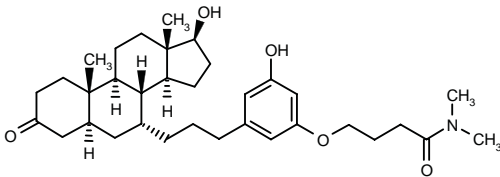
SOURCE – Yamanouchi.

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1. Hirano, M. et al. (Yamanouchi Pharmaceutical Co., Ltd.) *Propane-1,3-dione derivs.* WO 0202533.

315796

4-[3-Hydroxy-5-[3-[(5 α ,7 α ,17 β)-17-hydroxy-3-oxoandros-tan-7-yl]propyl]phenoxy]-*N,N*-dimethylbutyramide



C34 H51 N O5; Mol wt: 553.7789

ACTION – A representative compound from a series of steroid derivatives with antiandrogenic activity and devoid of hepatotoxicity and the liability for androgen resistance developing upon long-term administration. This compound suppressed dihydrotestosterone (DHT)-induced trans-cription of androgen receptors in HeLa cells with an IC₅₀ of 392 nM. Potentially useful for the treatment of prostate cancer, prostatic hypertrophy, male pattern baldness, acne vulgaris, seborrhea and hypertrichosis.

SOURCE – Chugai.

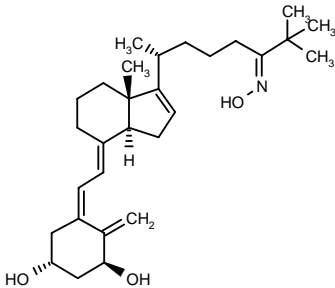
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BH-1625(NOH)TB-2

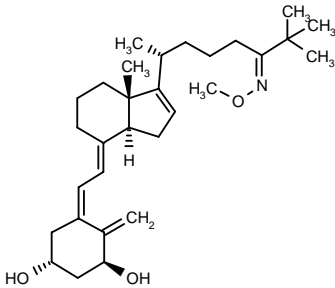
317925

(+)-1 α -Hydroxy-25-(hydroxyimino)-26,26,26-trimethyl-27-norvitamin D₃



C29 H45 N O3; Mol wt: 455.6785

ACTION – Oxime analogue of calcitriol with comparable antiproliferative activity in rat osteosarcoma ROS 17/2.8 cells (ED₅₀ = 2 and 0.4 nM, respectively) but low calcemic activity in rats at 0.5 μ g/kg/day for 7 days. Potentially useful as a cancer chemopreventive and chemothera-peutic, as well as for the treatment of psoriasis, osteoporosis and immune system disorders. Another related compound is:



BH-1625(NOMe)TB-2 [317926]: C30 H47 N O3

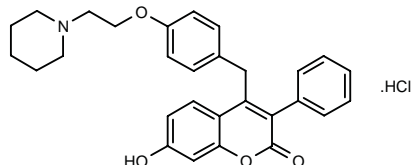
SOURCES – Johns Hopkins University, Baltimore, MD (US); M.D. Anderson Cancer Center, Houston, TX (US).

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SP-500263**307957**

7-Hydroxy-3-phenyl-4-[4-[2-(1-piperidinyl)ethoxy]benzyl]-2H-1-benzopyran-2-one hydrochloride



C29 H29 N O4 . HCl; Mol wt: 492.0120

ACTION – Potent and selective estrogen receptor modulator (SERM) with high affinity for both human estrogen ER α and ER β receptors (K_i = 1.4 and 7.3 nM, respectively). Compound showed functional selectivity for the ER α subtype in osteosarcoma U-2 OS cells expressing ER α receptors, where it inhibited the production of IL-6 (IC_{50} = 0.67 nM) and granulocyte-macrophage colony-stimulating factor (GM-CSF). Compound acted as an estrogen antagonist in breast cancer cells, inhibiting estrogen-dependent MCF-7 cell proliferation with an IC_{50} of about 8 nM. In mice bearing MCF-7 xenografts, doses of 3-30 mg/kg/day i.p. for 28 days reduced estrogen-stimulated tumor growth; maximum efficacy was reached at a dose of 30 mg/kg. In this model, compound was as effective as tamoxifen and superior to raloxifene at corresponding doses. Potentially useful for preventing the progression of breast cancer.

SOURCE – Signal (Celgene).

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1. Bhagwat, S.S. et al. (Signal Pharmaceuticals, Inc.) *Cpds. and methods for modulation of estrogen receptors*. WO 0149673.
2. Brady, H. et al. *Differential response of estrogen receptors α and β to SP500263, a novel potent selective estrogen receptor modulator*. Mol Pharmacol 2002, 61(3): 562.
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CANCER IMMUNOTHERAPY

DCs/CPP1-TRP2 VACCINE**316543**

Mature dendritic cells (DCs) loaded with an antigenic peptide derived from tyrosine-related protein 2 (TRP2) covalently linked to a cell-penetrating peptide 1 (CPP1), whose sequence is AAVLLPVLLAAPSPSYVYHQF

ACTION – Cancer vaccine consisting of dendritic cells (DC) pulsed with tumor antigen-derived CPP1 (cell-penetrating peptide 1) and TRP2 (tyrosine-related protein 2) peptides, able to generate potent antitumor immunity against poorly immunogenic melanoma B16 cells in animal models. The vaccine completely protected mice against subsequent challenge with B16 melanoma and

also significantly inhibited lung metastases in animals with established tumors; further experiments demonstrated that both CD4⁺ and CD8⁺ T-cells are required for DCs/CPP1-TRP2 to provide protective immunity.

SOURCE – Baylor College of Medicine, Houston, TX (US).

REFERENCES

1. Wang, R.-F. and Wang, H.Y. *Enhancement of antitumor immunity by prolonging antigen presentation on dendritic cells*. Nat Biotechnol 2002, 20(2): 149.

ZEVALIN™**320040**

ACTION – Immunoconjugate consisting of the murine monoclonal antibody ibritumomab linked through a stable thiourea covalent bond to the linker-chelator tiuxetan, able to bind to CD20 antigen on the surface of B-lymphocytes and B-cell tumors, inducing cellular damage and death.

INDICATION – To be used as part of a therapeutic regimen for the treatment of relapsed or refractory low-grade, follicular, or transformed B-cell non-Hodgkin's lymphoma (NHL) including patients with Rituxan® (rituximab)-refractory follicular NHL. The Zevalin™ therapeutic regimen consists of an infusion of rituximab preceding In-111 Zevalin™ [198486]*, followed at 7-9 days by a second rituximab infusion and subsequent administration of Y-90 Zevalin™ [198487]*.

PRESENTATION – Zevalin™ is supplied as 2 separate and distinctly labeled kits that contain all of the nonradioactive ingredients necessary to produce a single dose of In-111 Zevalin™ and a single dose of Y-90 Zevalin™. Each of the 2 Zevalin™ kits contains 4 vials that are used to produce a single dose of either In-111 Zevalin™ or Y-90 Zevalin™: 1) one Zevalin™ vial containing 3.2 mg of ibritumomab tiuxetan in 2 ml of 0.9% sodium chloride solution; 2) one 50-mM sodium acetate vial containing 13.6 mg of sodium acetate trihydrate in 2 ml of water for injection; 3) one formulation buffer vial containing 750 mg of albumin (human), 76 mg of sodium chloride, 21 mg of sodium phosphate dibasic heptahydrate, 4 mg of pentetic acid, 2 mg of potassium phosphate monobasic and 2 mg potassium chloride in 10 ml of water for injection adjusted to pH 7.1, with either sodium hydroxide or hydrochloric acid; 4) one empty reaction vial, sterile, pyrogen-free.

PROPRIETARY NAME – Zevalin (US).

SOURCES – Idec Pharmaceuticals; licensed to Schering AG for marketing outside the U.S.

RECENT REFERENCES

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2. Ansell, S.M. et al. *Subsequent chemotherapy regimens are well tolerated after radioimmunotherapy with Zevalin™ for non-Hodgkin lymphoma*. Blood 2001, 98(11, Part 1): Abst 2533.
3. Czuczman, M.S. et al. *Zevalin™ radioimmunotherapy in patients with pre-existing host humoral responses*. Blood 2001, 98(11, Part 2): Abst 4685.
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8. Flinn, I.W. et al. *The Zevalin radioimmunotherapy(RIT) regimen is active in heavily pretreated, bulky, rituximab refractory NHL.* Proc Am Soc Clin Oncol 2001, 20(Part 1): Abst 1141.

9. Gordon, L. et al. *High-dose therapy can be safely and successfully administered after Zevalin treatment.* Proc Am Soc Clin Oncol 2001, 20(Part 2): Abst 2681.

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30. *Idec prepares responses to FDA complete review letter for Zevalin.* DailyDrugNews.com (Daily Essentials) 2001, May 11.

31. *Idec reports status of select products.* DailyDrugNews.com (Daily Essentials) 2001, April 27.

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34. *Novel cancer therapy now available in U.S.* DailyDrugNews.com (Daily Essentials) 2002, March 26.

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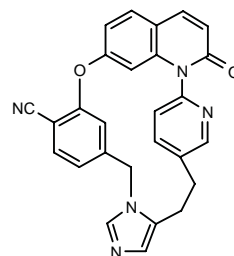
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*See In-PAN-B and Y-PAN-B Drug Data Rep 1993, 015(09): 0874.

INHIBITORS OF SIGNAL TRANSDUCTION PATHWAYS

315366

26-Oxo-19-oxa-1,3,10,12-tetraazahexacyclo-[18.6.2.2^{2,5}.1^{14,18}.0^{8,12}.0^{23,27}]hentriaconta-2,4,8,10,14(29),15,17,20,22,24,27,30-dodecaene-17-carbonitrile



C27 H19 N5 O2; Mol wt: 445.4801

ACTION – Macrocyclic inhibitor of protein farnesyltransferase and protein geranylgeranyltransferase type I. Potentially useful for the treatment of cancer (particularly cancer characterized by mutated K4B-Ras protein), as well as blindness associated with retinal vascularization, hepatitis delta virus infections, restenosis and polycystic kidney disease.

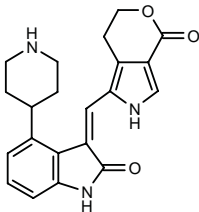
SOURCE – Merck & Co.

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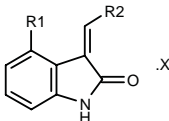
315425

1-[2-Oxo-4-(4-piperidiny)-2,3-dihydro-1 *H*-indol-3-ylidenemethyl]-2,4,6,7-tetrahydropyrano[3,4-*c*]pyrrol-4-one



C21 H21 N3 O3; Mol wt: 363.4149

ACTION – An inhibitor of protein kinases such as tyrosine and serine/threonine kinases including EGFR (epidermal growth factor receptor), PDGFR (platelet-derived growth factor receptor), IGFR (insulin-like growth factor receptor), Flk, cyclin-dependent kinases (CDKs), Met and Src, most particularly CDK2. The compound demonstrated *in vitro* activity against FGFR1 (IC₅₀ = 2.09 mM), GST-Flk1 (IC₅₀ = 0.51 mM), EGFR (IC₅₀ = 1.21 mM) and CDK2/cyclin A (IC₅₀ = 0.009 mM). Potentially useful for the treatment of cancer, as well as diabetes, immune and autoimmune disorders, hyperproliferative disorders, restenosis, fibrosis, psoriasis, von Hippel-Lindau syndrome, arthritis, angiogenesis, inflammation and cardiovascular diseases. Other exemplified indolinones are:



Compound	R1	R2	X	Formula
315428	4-Pyr	5-Me-4-imidazolyl		C ₁₈ H ₁₄ N ₄ O
315429	4-Pyr	4-oxo-2,4,6,7-tetrahydro-pyrano[3,4- <i>c</i>]pyrrol-1-yl		C ₂₁ H ₁₅ N ₃ O ₃
315431	4-Pyr	3-Me-4-(1-Pip-CO)-2-pyrrolyl		C ₂₅ H ₂₄ N ₄ O ₂
315433	4-Pip	5-Me-4-imidazolyl	.CH3CO2H	C ₁₈ H ₂₀ N ₄ O .C ₂ H ₄ O ₂
315434	4-Pip	3-Me-4-(1-Pip-CO)-2-pyrrolyl		C ₂₅ H ₃₀ N ₄ O ₂
315435	4-Pip	3-Me-4-(4-morpholinyl-CO)-1-pyrrolyl		C ₂₄ H ₂₈ N ₄ O ₃
315437	4-Pip	4-oxo-4,5,6,7-tetrahydro-2H-pyrrolo[3,4- <i>c</i>]pyridin-1-yl		C ₂₁ H ₂₂ N ₄ O ₂
315439	4-Pip	5-Me-4-oxo-4,5,6,7-tetrahydro-2H-pyrrolo[3,4- <i>c</i>]pyridin-1-yl		C ₂₂ H ₂₄ N ₄ O ₂
315440	4-Pip	5-(4-morpholinyl-CH2CH2O)-2-indolyl		C ₂₈ H ₃₂ N ₄ O ₃

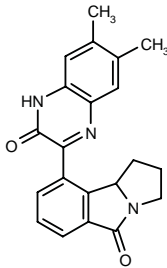
SOURCE – Sugen (Pharmacia).

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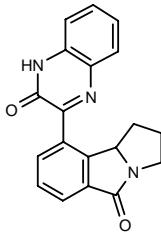
315484

9-(6,7-Dimethyl-3-oxo-3,4-dihydroquinoxalin-2-yl)-2,3,5,9b-tetrahydro-1 *H*-pyrrolo[2,1-*a*]isoindol-5-one



C21 H19 N3 O2; Mol wt: 345.4001

ACTION – An inhibitor of cyclin-dependent kinases CDK4 and CDK6 with IC₅₀ values of 0.13 and 0.088 μM, respectively, against CDK4/cyclin D2 and CDK6/cyclin D3. Compound was also shown to inhibit the proliferation of human glioblastoma T98G (IC₅₀ = 0.18 μM) and osteogenic sarcoma U-2 OS cells (IC₅₀ = 0.21 μM). Potentially useful for the treatment of solid tumors. Another exemplified pyrazinone derivative is:



315485: C19 H15 N3 O2

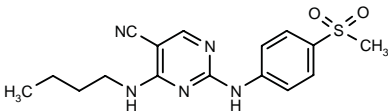
SOURCE – Banyu.

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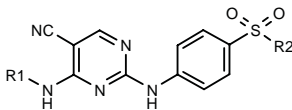
315563

4-(Butylamino)-2-[4-(methylsulfonyl)phenylamino]-pyrimidine-5-carbonitrile



C16 H19 N5 O2 S; Mol wt: 345.4251

ACTION – Potential antitumor agent, a selective inhibitor of the cyclin-dependent kinases CDK2, CDK4 and/or CDK6. Compound may also be useful for the treatment of other proliferative diseases including psoriasis, rheumatoid arthritis, Kaposi’s sarcoma, hemangioma, acute and chronic nephropathies, atherosclerosis, arterial restenosis, autoimmune diseases, inflammation, bone diseases and ocular diseases with retinal vessel proliferation. Other specifically claimed pyrimidine derivatives are:



Compound	R1	R2	Formula
315567	Et	NHCH2CH2OMe	C ₁₆ H ₂₀ N ₆ O ₃ S
315568	Et	NH(CH2)3OMe	C ₁₇ H ₂₂ N ₆ O ₃ S
315569	cyclopropyl	NHCH2CH2OMe	C ₁₇ H ₂₀ N ₆ O ₃ S
315570	cyclopropyl	NH(CH2)3OMe	C ₁₈ H ₂₂ N ₆ O ₃ S
315571	cyclopropyl	Et	C ₁₆ H ₁₇ N ₅ O ₂ S
315573	cyclopropyl	Me	C ₁₅ H ₁₅ N ₅ O ₂ S
315574	Et	NHMe	C ₁₄ H ₁₆ N ₆ O ₂ S
315575	cyclopropyl	N(Me)CH2CH2OMe	C ₁₈ H ₂₂ N ₆ O ₃ S
315576	Et	Et	C ₁₅ H ₁₇ N ₅ O ₂ S

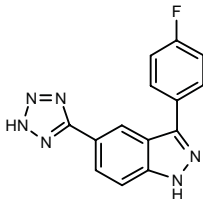
SOURCE – AstraZeneca.

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1. Thomas, A.P. et al. (AstraZeneca AB;AstraZeneca plc) *Pyrimidine derivs.* WO 0204429.

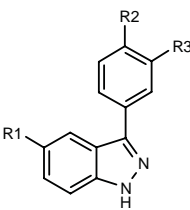
316884

3-(4-Fluorophenyl)-5-(2*H*-tetrazol-5-yl)-1*H*-indazole



C14 H9 F N6; Mol wt: 280.2651

ACTION – c-Jun N-terminal kinase (JNK) inhibitor with an IC₅₀ below 0.5 μM for inhibition of JNK2. Potentially useful for the treatment of cancer, rheumatoid arthritis, asthma, inflammatory bowel disease, atherosclerosis, postangioplasty restenosis, left ventricular hypertrophy, myocardial infarction, stroke, ischemic organ damage, transplant rejection, organ preservation, multiple organ failure, epilepsy, Alzheimer’s disease, Parkinson’s disease, immune response to bacterial or viral infection, arthritis, asthma, chronic obstructive pulmonary disease, multiple sclerosis, type 2 diabetes, etc. Other exemplified indazole derivatives include the following:



Compound	R1	R2	R3	Formula
316885	5-i-Pr-2 <i>H</i> -1,2,4-triazol-3-yl	F	H	C ₁₈ H ₁₆ FN ₅
316886	5-tetrazolyl	Cl	H	C ₁₄ H ₉ ClN ₆
316887	4 <i>H</i> -1,2,4-triazol-3-yl	H	NHCOCH2OMe	C ₁₈ H ₁₈ N ₆ O ₂
316888	2 <i>H</i> -tetrazol-5-yl	H	1-Pip-CH2CH2CONH	C ₂₂ H ₂₄ N ₆ O
316889	2 <i>H</i> -tetrazol-5-yl	H	(<i>S</i>)-NHCOCH(OH)Me	C ₁₇ H ₁₅ N ₇ O ₂
316890	1,2,4-triazol-3-yl	H	2-Pyr-CONH	C ₂₁ H ₁₅ N ₇ O
316891	3-[N(Me)2CH2]-1 <i>H</i> -1,2,4-triazol-5-yl	H	CONHPh	C ₂₅ H ₂₃ N ₇ O
316892	1,2,4-triazol-3-yl	H	CONHPh	C ₂₂ H ₁₈ N ₆ O

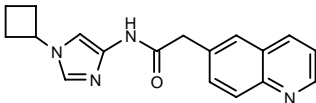
SOURCE – Signal (Celgene).

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1. Bhagwat, S.S. et al. (Signal Pharmaceuticals, Inc.) *Indazole derivs. as JNK inhibitors and compsns. and methods related thereto.* WO 0210137.

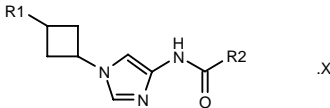
316903

N-(1-Cyclobutyl-1*H*-imidazol-4-yl)-2-(6-quinolinyl)acetamide

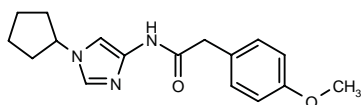


C18 H18 N4 O; Mol wt: 306.3672

ACTION – An inhibitor of the cyclin-dependent kinases CDK2 and CDK5 and the glycogen synthase kinase GSK-3. Potentially useful for the treatment of cancer, as well as male infertility, diabetes, impaired glucose tolerance, syndrome X, polycystic ovary syndrome, obesity, frailty, acute sarcopenia, sepsis, hair loss and immunodeficiency. Other exemplified compounds are:



Compound	R1	R2	Isomer	X	Formula
316905	Ph	CH2-6-quinolinyl	cis		C ₂₄ H ₂₂ N ₄ O
316906	H	OPh			C ₁₄ H ₁₅ N ₃ O ₂
316907	H	NH-5-isoquinolinyl			C ₁₇ H ₁₇ N ₅ O
316908	NH2	1-Naph-CH2	cis		C ₁₉ H ₂₀ N ₄ O
316910	6-Me-2-Pyr-CONH	1-Naph-CH2	cis		C ₂₆ H ₂₅ N ₅ O ₂
316911	NHCO-2-quinolinyl	1-Naph-CH2	cis		C ₂₉ H ₂₅ N ₅ O ₂
316912	4-Pip-CONH	1-Naph-CH2	cis	HCl	C ₂₅ H ₂₉ N ₅ O ₂ ·HCl
316913	NHAc	1-Naph-NH	cis		C ₂₀ H ₂₁ N ₅ O ₂



316904: C17 H21 N3 O2

SOURCE – Pfizer.

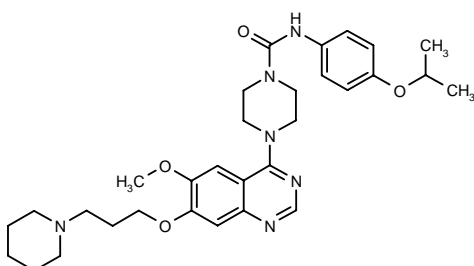
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- Ahlijanian, M.K. et al. (Pfizer Products Inc.) *Imidazole derivs.* WO 0210141.

CT-53518¹⁻⁴

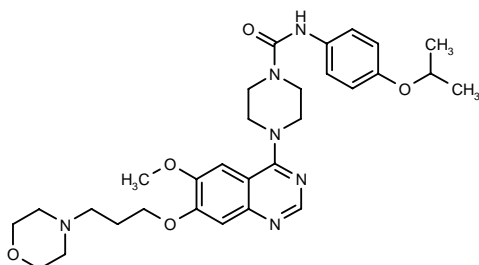
312325

N-(4-Isopropoxyphenyl)-4-[6-methoxy-7-[3-(1-piperidinyl)-propoxy]quinazolin-4-yl]piperazine-1-carboxamide



C31 H42 N6 O4; Mol wt: 562.7108

ACTION – Potent and selective inhibitor of Flt-3 receptor protein kinase (IC_{50} = 0.22 μ M in an autophosphorylation assay) that also inhibits platelet-derived growth factor receptor (PDGFR) and c-kit protein kinases (IC_{50} = 0.20 and 0.17 μ M, respectively). Compound inhibited the autophosphorylation of wild-type Flt-3 and a constitutively activated Flt-3 with internal tandem duplications at nanomolar concentrations (IC_{50} = 30-100 nM). *In vivo*, it was metabolically stable and showed good oral bioavailability (> 50%) and a long half-life. Compound increased survival in a mouse model of Flt-3-mediated leukemia after oral administration. Another related compound is:



CT-53608 [317801]^{1,2}: C30 H40 N6 O5

SOURCES – Kyowa Hakko; Millennium.

REFERENCES

- Pandey, A. et al. (COR Therapeutics, Inc.; Kyowa Hakko Kogyo Co., Ltd.) *Quinazoline derivs. as kinase inhibitors.* WO 0216351.
- Pandey, A. et al. *Discovery of CT53518, a potent and oral inhibitor of FLT3 kinase targeted for the treatment of acute myelogenous leukemia.* 223rd ACS Natl Meet (April 7-11, Orlando) 2002, Abst MEDI 19.

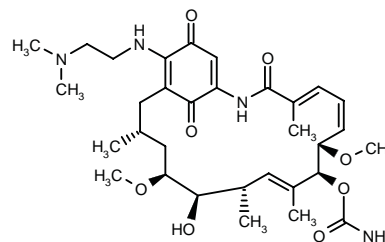
- Yu, J. et al. *CT53518, a specific Flt3 kinase inhibitor selectively blocks mitogenic and survival signaling pathways and induces apoptosis in human AML cells that harbor a Flt3/ITD mutation.* Proc Amer Assoc Cancer Res 2002, 43: Abst LB-27.

- Millennium and Cor Therapeutics announce merger plans. DailyDrugNews.com (Daily Essentials) 2001, Dec 12.

NSC-707545

317446

17-Demethoxy-17-[2-(dimethylamino)ethylamino]-geldanamycin



C32 H48 N4 O8; Mol wt: 616.7512

ACTION – Geldanamycin analogue, a selective inhibitor of the oncoprotein p185^{erbB2} with strong growth-inhibitory activity against the NCI 60 tumor cell panel (GI_{50} = 51 nM), as well as *in vivo* activity against human breast cancer MDA-MB-231, lung cancer NCI-H22 and melanoma LOX IMVI xenografts. Pharmacokinetic studies in rodents showed excellent i.p. and good oral bioavailability (100 and 50%, respectively) in mice, wide tissue distribution in rats and mice with the exception of brain and testes, and modest metabolism. No toxicity was seen in mice treated with an i.v. bolus dose of 75 mg/kg.

SOURCES – National Cancer Institute, Bethesda, MD (US); University of Pittsburgh, Pittsburgh, PA (US).

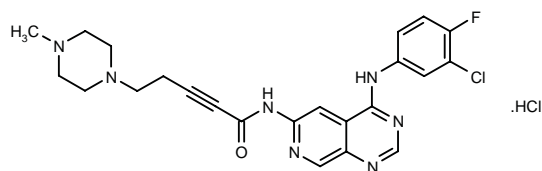
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- Egorin, M.J. et al. *Pharmacokinetics, tissue distribution, and metabolism of 17-(dimethylaminoethylamino)-17-demethoxygeldanamycin (NSC 707545) in CD2F1 mice and Fischer 344 rats.* Cancer Chemother Pharmacol 2002, 49(1): 7.
- Lan, J. et al. *Pharmacokinetics and pharmacodynamic effects of 17-(dimethylaminoethylamino)-17-demethoxygeldanamycin (NSC 707545) on heat shock proteins and Raf-1 in mice.* Proc Amer Assoc Cancer Res 2002, 43: Abst 1646.

PD-205520

317927

N-[4-(3-Chloro-4-fluorophenylamino)pyrido[3,4-*d*]pyrimidin-6-yl]-5-(4-methylpiperazin-1-yl)-2-pentynamide hydrochloride



C23 H23 Cl F N7 O . HCl; Mol wt: 504.3946

ACTION – Irreversible inhibitor of erb-B (epidermal growth factor [EGF] receptor) receptor tyrosine kinase with efficacy in preclinical tumor models in rodents. Studies of systemic toxicity in rats following oral administration for 4 weeks (5, 15 and 45 mg/kg) showed that the major toxicities of compound affected the skin and gastrointestinal tract, consistent with its mechanism of action.

SOURCE – Pfizer.

REFERENCES

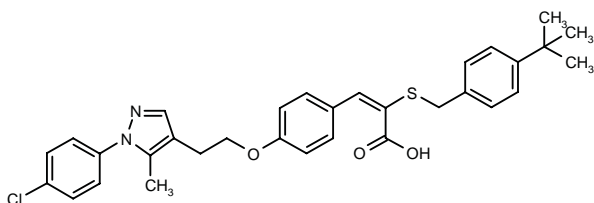
1. Bridges, A.J. et al. (Pfizer Inc.) *Irreversible inhibitors of tyrosine kinases*. JP 2000508657, US 6344459, WO 9738983.

2. Brown, A.P. et al. *Toxicity of an irreversible erb-B tyrosine kinase receptor inhibitor in rats*. Proc Amer Assoc Cancer Res 2002, 43: Abst 3896.

TPY-835

317870

2-(4-*tert*-Butylbenzylsulfanyl)-3-[4-[2-[1-(4-chlorophenyl)-5-methyl-1*H*-pyrazol-4-yl]ethoxy]phenyl]-2-propenoic acid



C32 H33 Cl N2 O3 S; Mol wt: 561.1427

ACTION – Antineoplastic agent, a derivative of cinnamic acid shown to inhibit cell cycle-regulating Cdc25 dual-specificity phosphatase activity, with an IC₅₀ value of 5 µM against Cdc25A and Cdc25B; it was inactive against Cdc25C and several other phosphatases. Compound inhibited the growth of several cancer cells *in vitro* including drug-resistant cell lines, suppressed activation of CDK2 and phosphorylation of pRB, and induced cell cycle arrest in the G₁ phase. In mice bearing human lung carcinoma A549 cells, compound showed modest antitumor activity on its own but strongly potentiated the effect of 5-fluorouracil.

SOURCE – Taiho.

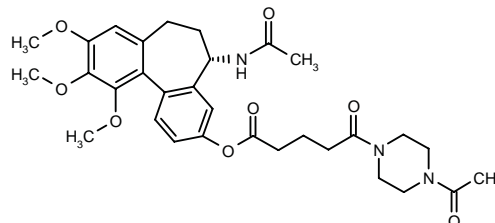
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ANGIOGENESIS INHIBITORS

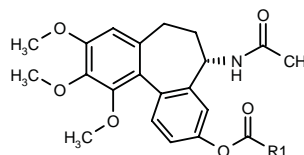
315637

5-(4-Acetylpiperazin-1-yl)-5-oxopentanoic acid 5(*S*)-acetamido-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-3-yl ester



C31 H39 N3 O8; Mol wt: 581.6621

ACTION – Agent with antiangiogenic activity able to induce tumor necrosis following administration to mice bearing *H-ras*-transfected NIH/3T3 fibroblasts. Potentially useful for damaging newly formed vascular endothelium in the treatment of cancer, as well as other diseases associated with angiogenesis such as diabetes, psoriasis, rheumatoid arthritis, Kaposi's sarcoma, hemangioma, acute and chronic nephropathies, atheroma, arterial restenosis, autoimmune diseases, acute inflammation, endometriosis, dysfunctional uterine bleeding and ocular diseases with retinal vessel proliferation. Other exemplified colchicolin derivatives are:



Compound	R1	Formula
315639	4-Ac-1-Piz-COCH2CH2	C ₃₀ H ₃₇ N ₃ O ₈
315640	3-(4-Ac-1-Piz-CH2)-Ph	C ₃₄ H ₃₉ N ₃ O ₇
315641	4-(4-Me-1-Piz-CH2CH2CONH)-Ph	C ₃₅ H ₄₂ N ₄ O ₇
315642	3-[4-(NH2CO)-1-Piz-CH2]-Ph	C ₃₃ H ₃₈ N ₄ O ₇
315643	1-Ac-4-Pip	C ₂₈ H ₃₄ N ₂ O ₇
315646	CH2CH2CON(CH2CH2OH)2	C ₂₈ H ₃₆ N ₂ O ₉
315647	(CH2)3CON(CH2CH2OH)2	C ₂₉ H ₃₈ N ₂ O ₉

SOURCE – Angiogene Pharmaceuticals.

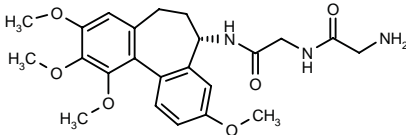
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316531

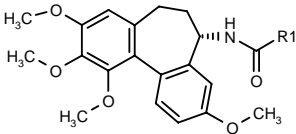
2-Amino-*N*-[*N*-[3,9,10,11-tetramethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-5(*S*)-yl]carbamoylmethyl]-acetamide

Glycyl-glycine [3,9,10,11-tetramethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-5(*S*)-yl]amide



C23 H29 N3 O6; Mol wt: 443.4971

ACTION – Antiangiogenic agent, potentially useful as a vascular-damaging agent in the treatment of cancer (particularly solid tumors), diabetes, psoriasis, rheumatoid arthritis, Kaposi’s sarcoma, hemangioma, acute and chronic nephropathies, atheroma, arterial restenosis, autoimmune diseases, acute inflammation, endometriosis, dysfunctional uterine bleeding and ocular diseases with retinal vessel proliferation. Other exemplified colchicol derivatives are:



Compound	R1	Formula
316533	(CH2)3OPO3Na2	C ₂₃ H ₂₈ NNa ₂ O ₉ P
316534	1-imidazolyl-CH2CH2NH	C ₂₅ H ₃₀ N ₄ O ₅
316535	OCH2CH2OPO3Na2	C ₂₂ H ₂₆ NNa ₂ O ₁₀ P
316536	4-morpholinyl-CH2CH2O	C ₂₆ H ₃₄ N ₂ O ₇
316537	4-Me-1-Piz-(CH2)3O	C ₂₈ H ₃₈ N ₃ O ₆
316538	4-Ac-1-Piz-CH2CH2O	C ₂₈ H ₃₇ N ₃ O ₇
316539	4-Me-1-Piz-CO-CH2CH2	C ₂₈ H ₃₇ N ₃ O ₆
316540	4-Ac-1-Piz-(CH2)3O	C ₂₉ H ₃₉ N ₃ O ₇
316541	4-morpholinyl-CO(CH2)3O	C ₂₈ H ₃₆ N ₂ O ₈
316542	4-Me-1-Piz-CO(CH2)3O	C ₂₉ H ₃₉ N ₃ O ₇

SOURCE – Angiogene Pharmaceuticals.

REFERENCES

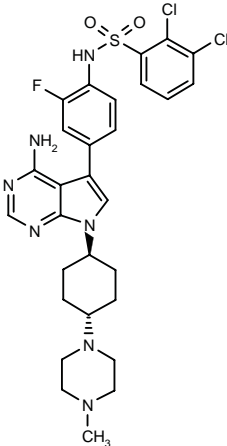
1. Arnould, J.C. (Angiogene Pharmaceuticals Ltd.) *Colchicol derivs. as angiogenesis inhibitors*. WO 0208213.

A-422885.66

317941

N-[4-[4-Amino-7-[*trans*-4-(4-methylpiperazin-1-yl)cyclohexyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]-2-fluorophenyl]-2,3-dichlorobenzenesulfonamide

BSF-466895



C29 H32 Cl2 F N7 O2 S; Mol wt: 632.5888

ACTION – Antiangiogenic agent, a potent and selective inhibitor of Tie-2 kinase (IC₅₀ = 5 nM in the presence of ATP; K_i = 1 nM) with 30-1,000-fold selectivity over other kinases. Compound inhibited Tie-2 autophosphorylation in NIH/3T3 cells transfected with human Tie-2 (I₅₀ = 5 nM) and in the same cells implanted into mice, where a dose of 25 mg/kg i.v. produced a 40-90% reduction in Tie-2 autophosphorylation for up to 18 h. Moreover, compound exhibited antiangiogenic activity *in vitro* in the rat aortic ring assay (IC₉₀ = 100 nM) and *in vivo* in a Matrigel implant assay, where doses of 3-50 mg/kg i.v. for 4 days inhibited vessel formation by up to 74%. Potentially useful for the treatment of tumor growth/metastasis, as well as rheumatoid arthritis.

SOURCE – Abbott.

REFERENCES

1. Bump, N.J. et al. (BASF AG) *Method of identifying inhibitors of Tie-2*. WO 0172778.

2. Hirst, G.C. et al. (BASF AG) *Pyrrolopyrimidines as protein kinase inhibitors*. EP 1114053, WO 0017203.

3. Hirst, G.C. et al. (BASF AG) *Pyrrolopyrimidines as tyrosine kinase inhibitors*. WO 0172751.

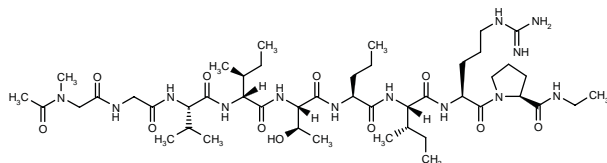
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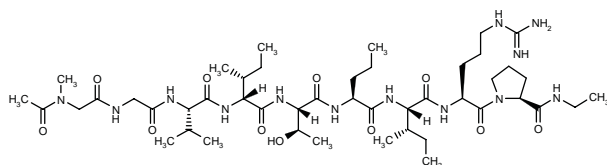
ABT-510¹⁻⁴**300354**

N-Acetyl-*N*-methyl-glycyl-glycyl-L-valyl-D-alloisoleucyl-L-threonyl-L-norvalyl-L-isoleucyl-L-argininyl-L-proline *N*-ethylamide



C46 H83 N13 O11; Mol wt: 994.2417

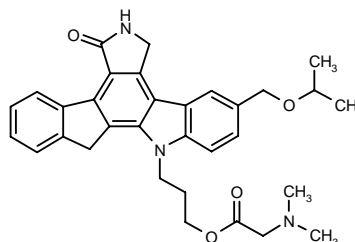
ACTION – Thrombospondin-1 mimetic peptide with potent antiangiogenic activity *in vitro* and *in vivo*. Compound inhibited vascular endothelial growth factor (VEGF)-stimulated human microvascular endothelial cell migration with an IC₅₀ of 0.03 nM and also inhibited endothelial cell tube formation and increased apoptosis. In a mouse corneal model of angiogenesis, compound inhibited basal fibroblast growth factor (bFGF)-induced neovascularization when delivered continuously by s.c. pump at 30 mg/kg/day. In nude mice bearing human breast cancer MDA-MB-435 xenografts, compound given as a continuous s.c. infusion of 0.3 mg/kg/day or as a single bolus dose of 3 mg/kg/day produced a 50% decrease in tumor growth. Currently undergoing phase I trials. Another related compound is:

**ABT-526 [317851]¹⁻³**: C46 H83 N13 O11**SOURCE** – Abbott.**REFERENCES**

1. Henkin, J. et al. (Abbott Laboratories Inc.) *Peptide antiangiogenic drugs*. WO 9961476.
2. Haviv, F. et al. *Thrombospondin-1 mimetic peptides as inhibitors of angiogenesis*. Proc Amer Assoc Cancer Res 2002, 43: Abst 3665.
3. Henkin, J. et al. *Tumor inhibition by anti-angiogenic TSP-1 mimetic peptides*. Proc Amer Assoc Cancer Res 2002, 43: Abst 904.
4. *Abbott Laboratories*. Merrill Lynch Global Healthcare Conf (Feb 6-8, New York) 2001, .

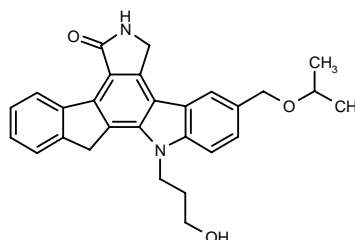
CEP-7055^{1,2,4,6-10}**312858**

N,N-Dimethylglycine 3-[9-(isopropoxymethyl)-5-oxo-5,6,7,13-tetrahydro-12*H*-indeno[2,1-*a*]pyrrolo[3,4-*c*]-carbazol-12-yl]propyl ester



C32 H35 N3 O4; Mol wt: 525.6455

ACTION – Antiangiogenic agent, an oral prodrug of the potent and selective inhibitor of human vascular endothelial growth factor receptor (VEGFR) kinase **CEP-5214**, which showed IC₅₀ values of 12-18 nM against VEGFR2/KDR, VEGFR1/Flt-1 and VEGFR3/Flt-4 kinases. The prodrug exhibited significant antitumor efficacy in a range of murine and human tumor xenograft models in mice (melanoma A375, glioblastoma U-251 MG and U-87 MG, lung carcinoma Calu-6, pancreatic carcinoma AsPC-1, angiosarcoma SVR) following chronic oral administration, with a minimum effective dose of 3 mg/kg b.i.d. Its activity was independent of initial tumor volume and reversible upon discontinuation of treatment, and it was not associated with systemic toxicity after chronic oral administration. Compound is now undergoing phase I clinical trials in cancer patients.

**CEP-5214 [279113]¹⁻⁶**: C28 H28 N2 O3,**SOURCES** – Cephalon; Sanofi-Synthélabo.**REFERENCES**

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2. Jones-Bolin, S. et al. *The effects of the orally-active VEGF-R kinase inhibitor, CEP-7055, on primary tumor growth and metastatic profile in orthotopic models of human pancreatic ductal carcinoma and murine renal carcinoma (RENCA) in mice*. Proc Amer Assoc Cancer Res 2002, 43: Abst 2601.
3. Levis, M.J. et al. *FLT3-targeted inhibitors kills FLT3-dependent modeled cells, leukemia-derived cell lines, and primary AML blasts in vitro and in vivo*. Blood 2001, 98(11, Part 1): Abst 3010.
4. Mallamo, J.P. et al. *Identification, SAR and preclinical development of a novel inhibitor of VEGF-dependent angiogenesis: CEP-7055*. 223rd ACS Natl Meet (April 7-11, Orlando) 2002, Abst MEDI 21.
5. Pili, R. et al. *CEP-5214, a novel orally active inhibitor of vascular endothelial growth factor (VEGF) receptor tyrosine kinases, inhibits VEGF-induced angiogenesis and prostate tumor growth in vivo*. AACR-NCI-EORTC Int Conf Mol Targets Cancer Ther (Oct 29-Nov 2, Miami Beach) 2001, Abst 27.

6. Ruggeri, B.A. et al. *CEP-7055: An orally-active VEGF-R kinase inhibitor with potent anti-angiogenic activity and anti-tumor efficacy against human tumor xenograft growth*. Proc Amer Assoc Cancer Res 2002, 43: Abst 5347.

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8. *R&D portfolio*. Sanofi-Synthelabo Web Site 2002, March 1.

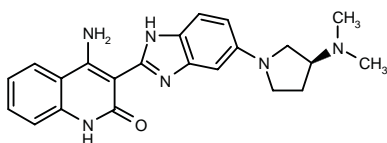
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CHIR-200131

317841

4-Amino-3-[5-[3(S)-(dimethylamino)pyrrolidin-1-yl]-benzimidazol-2-yl]-1,2-dihydroquinolin-2-one



C22 H24 N6 O; Mol wt: 388.4726

ACTION – Orally active tyrosine kinase inhibitor with respective IC_{50} values of 12, 7, 13, 8 and 51 nM against vascular endothelial growth factor receptor VEGFR1, VEGFR2 and VEGFR3, fibroblast growth factor receptor (FGFR) and platelet-derived growth factor receptor (PDGFR) kinases. Compound inhibited VEGF-mediated human microvascular endothelial cell (HMVEC) proliferation (IC_{50} = 43 nM) and showed an antiangiogenic effect against VEGF- or basic fibroblast growth factor (bFGF)-mediated endothelial cell migration, tube formation and vessel sprouting from rat aortic rings. Antiproliferative activity was seen against a panel of tumor cell lines including human colon cancer KM12L4a and murine breast cancer 4T1 cells (IC_{50} = 12 and 120 nM, respectively). *In vivo*, compound exhibited significant antiangiogenic activity in a Matrigel model in mice (92% reduction of angiogenesis at 100 mg/kg/day p.o.) and antitumor activity in subcutaneous tumor xenografts (KM12L4a colon and DU 145 and PC-3 prostate cells) and in murine models of spontaneous lung and liver metastases. The oral bioavailability of compound was at least 90% in mice and rats, 17% in dogs and 28% in monkeys, and it displayed an elimination half-life of 1.5-5.5 h after i.v. administration. *In vitro* experiments in Caco-2 cells indicated that compound has high intestinal permeability and is not a substrate for efflux proteins.

SOURCE – Chiron.

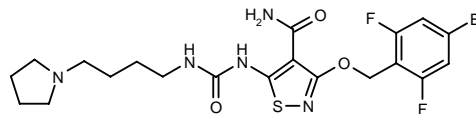
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- Wiesmann, M. et al. *Characterization of potent tyrosine kinase inhibitors that modulate angiogenesis and proliferation of selected cancer cell lines*. Proc Amer Assoc Cancer Res 2002, 43: Abst 4208.

CP-547632*

283989

3-(4-Bromo-2,6-difluorobenzyloxy)-5-[3-[4-(1-pyrrolidinyl)-butyl]ureido]isothiazole-4-carboxamide



C20 H24 Br F2 N5 O3 S; Mol wt: 532.4076

ACTION – Potent and selective inhibitor of vascular endothelial growth factor receptor-2 (VEGFR2) tyrosine kinase (IC_{50} = 11 nM), able to inhibit VEGF-stimulated VEGFR2 autophosphorylation in whole cells (IC_{50} = 5 nM) and VEGF-stimulated human umbilical vein endothelial cell (HUVEC) proliferation. In mice bearing NIH/3T3 H-ras-transformed embryonic fibroblasts, compound inhibited VEGFR2 phosphorylation in a dose-dependent manner with an ED_{50} of approximately 50 mg/kg p.o. Antitumor activity was demonstrated in human colon tumor Colo-205 and DLD-1 xenografts and human breast tumor MDA-MB-231 xenografts following doses of 12.5-100 mg/kg p.o. once or twice daily, and it also reduced microvessel density in colon tumors. Preliminary data from a phase I dose-escalation trial evaluating continuous daily oral treatment with CP-547632 in patients with advanced solid tumors demonstrated no dose-limiting toxicity and a long plasma half-life.

SOURCES – OSI Pharmaceuticals; Pfizer.

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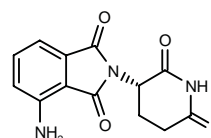
*Identified compound **283989** Drug Data Rep 2000, 022(02): 0186.

ENMD-0995*

277394

(-)-4-Amino-2-[2,6-dioxopiperidin-3(S)-yl]-1,2-dihydroisoindole-1,3-dione

S-3APG



C13 H11 N3 O4; Mol wt: 273.2469

ACTION – Thalidomide derivative with strong antiangiogenic and antiproliferative activity against myeloma cells ($IC_{50} \sim 10$ nM) including resistant strains. It was significantly more potent than thalidomide in inhibiting basic fibroblast growth factor (bFGF)- and vascular endothelial growth factor (VEGF)-induced corneal vascularization. In SCID mice bearing dexamethasone-resistant myeloma (MM.1R cells), compound (50 mg/kg) produced significant tumor regression and prolonged survival compared to thalidomide. Furthermore, it was effective in mice bearing RPMI-8226 myeloma, which was resistant to the drug *in vitro*, apparently due to an antiangiogenic effect. Antitumor activity was seen after both i.p. and p.o. administration. Preclinical toxicity studies in rats demonstrated no adverse effects at a dose equivalent to 1800 mg/m² in humans.

SOURCES – Celgene; EntreMed.

REFERENCES

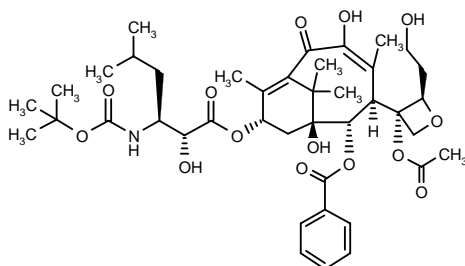
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*Identified compound **277394** Drug Data Rep 1999, 021(08): 0720.

IDN-5390

302054

2-*O*-Acetyl-1,3-anhydro-2-*C*-[(1*S*,2*S*,3*R*,9*S*)-2-(benzoyloxy)-9-[3(*S*)-(tert-butoxycarboxamido)-2(*R*)-hydroxy-5-methylhexanoyloxy]-1,5-dihydroxy-4,8,11,11-tetramethyl-6-oxobicyclo[5.3.1]undeca-4,7-dien-3-yl]-4-deoxy-D-erythro-pentitol



C41 H57 N O14; Mol wt: 787.8943

ACTION – Taxane derivative with antiangiogenic and antimetastatic activity, demonstrating a strong inhibitory effect on the migration of human umbilical vein endothelial cells (HUVEC) comparable to paclitaxel ($IC_{50} = 67$ and 64 nM, respectively) and slightly less antiproliferative activity than paclitaxel against a panel of human cancer cell lines including ovarian, breast and colon cancer and glioblastoma cells. *In vivo*, compound significantly inhibited FGF-2-induced angiogenesis in mice implanted with FGF-2-containing Matrigel pellets. Following daily s.c. injections 5 days/week, compound exhibited dose-dependent antitumor activity against several human tumor xenografts including ovarian and colon carcinoma and

glioblastoma, in the absence of local or systemic toxicity; in contrast, paclitaxel showed variable antitumor activity and substantial toxicity. Pharmacokinetic experiments indicated rapid absorption, with peak plasma levels reached within 30 min, rapid distribution and elimination, with a terminal half-life of 1 h following oral administration. Compound was detectable in plasma for up to 4 h after the maximum tolerated dose (MTD).

SOURCES – Indena; Istituto di Ricerche Farmacologiche Mario Negri, Milano (IT).

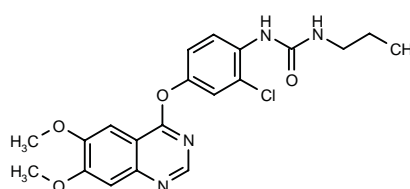
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KRN-633

317842

N-[2-Chloro-4-(6,7-dimethoxyquinazolin-4-yloxy)phenyl]-*N'*-propylurea



C20 H21 Cl N4 O4; Mol wt: 416.8629

ACTION – Small-molecule inhibitor of vascular endothelial growth factor receptor (VEGFR) tyrosine kinase ($IC_{50} = 1.2$ and 12 nM for inhibition of VEGFR1 and VEGFR2, respectively, in human umbilical vein endothelial cells [HUVEC]), inactive against epidermal growth factor (EGF) receptor, fibroblast growth factor (FGF) receptor or c-Met phosphorylation at up to 10 μ M. Compound blocked VEGF-induced, but not FGF-induced, activation of mitogen-activated protein kinase (MAPK) and HUVEC proliferation. Although it had no antiproliferative effect *in vitro* against various tumor cells, it exhibited oral antitumor and antiangiogenic effects in human tumor xenograft models including non-small cell lung carcinoma A549, hormone-independent prostate cancer DU 145 and colon cancer HT-29 xenografts. Significant antitumor activity was also seen against a human glioma xenograft at a dose of 20 mg/kg/day p.o.

SOURCE – Kirin Brewery.

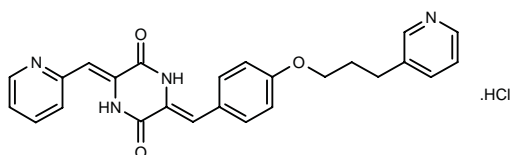
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4. Nakamura, K. et al. *In vitro characterization of KRN633, a novel small molecule inhibitor of VEGF receptor tyrosine kinases.* Proc Amer Assoc Cancer Res 2002, 43: Abst 876.

XR-5967

310300

3-(Pyridin-2-ylmethylene)-6-[4-[3-(3-pyridyl)propoxy]-benzylidene]piperazine-2,5-dione hydrochloride



C25 H22 N4 O3 . HCl; Mol wt: 462.9347

ACTION – Low-molecular-weight inhibitor of plasminogen activator inhibitor-1 (PAI-1) able to concentration-dependently inhibit the formation of the complex between recombinant human PAI-1 and urinary plasminogen activator (uPA), with an IC_{50} of 0.8 μ M, and to significantly inhibit the invasion and migration of human fibrosarcoma HT-1080 cells. In an *in vitro* model of angiogenesis, compound inhibited tubule formation by human endothelial cells by up to 77% at 5 μ M, whereas it had no effect on the adhesion of these cells to vitronectin.

SOURCE – Xenova.

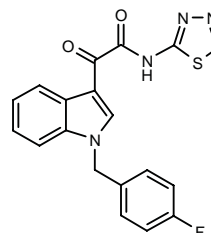
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3. *Accelerated progress marks Q3 at Xenova.* DailyDrugNews.com (Daily Essentials) 2001, Nov 26.

OTHER ONCOLYTIC DRUGS

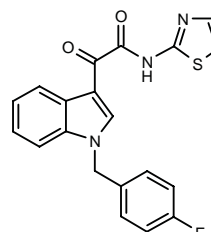
316377

2-[1-(4-Fluorobenzyl)-1*H*-indol-3-yl]-2-oxo-*N*-(1,3,4-thiadiazol-2-yl)acetamide



C19 H13 F N4 O2 S; Mol wt: 380.4017

ACTION – Antitumor agent for the treatment of solid tumors, particularly colon and lung cancer. Another exemplified 2-(1*H*-indol-3-yl)-2-oxoacetic acid derivative is:



316382: C20 H14 F N3 O2 S

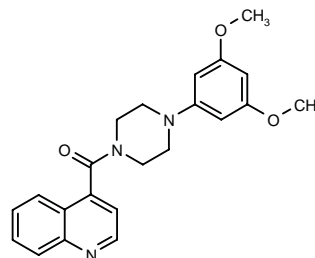
SOURCE – Novuspharma.

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316414

1-[4-(3,5-Dimethoxyphenyl)piperazin-1-yl]-1-(4-quinolin-yl)methanone



C22 H23 N3 O3; Mol wt: 377.4417

ACTION – Antineoplastic agent, a representative compound from a series of quinoline derivatives.

SOURCE – Zentaris.

REFERENCES

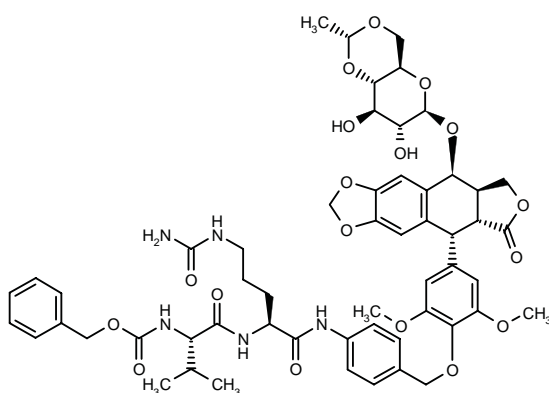
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318274

N-(Benzyloxycarbonyl)-L-valyl-*N*¹-[4-[[(5*R*,5*aR*,8*aR*,9*S*)-9-[(2*R*,4*aR*,6*R*,7*R*,8*R*,8*aS*)-7,8-dihydroxy-2-methylperhydropyrano[3,2-*d*][1,3]dioxin-6-yloxy]-6-oxo-5,5*a*,6,8,8*a*,9-hexahydrofuro[3',4':6,7]-naphtho[2,3-*d*][1,3]dioxol-5-yl]-2,6-dimethoxyphenoxy-methyl]phenyl]-*N*⁵-carbamoyl-L-ornithinamide

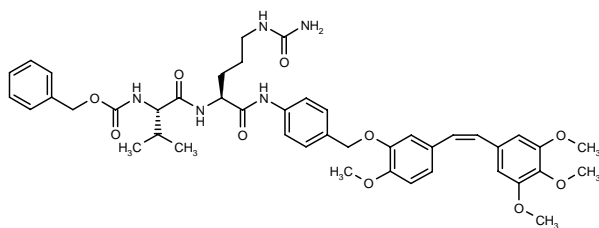
4'-*O*-[4-[*N*-(Benzyloxycarbonyl)-L-valyl-L-citrullylamino]-benzyl]etoposide

4'-*O*-[4-[*N*-(Benzyloxycarbonyl)-L-valyl-*N*⁵-carbamoyl-L-ornithylamino]benzyl]etoposide



C55 H65 N5 O18; Mol wt: 1084.1350

ACTION – Anticancer prodrug consisting of etoposide attached to the Z-Val-Cit-*p*-amidobenzyl alcohol through an ether linkage; it was stable in aqueous buffer and serum and was hydrolyzed by cathepsin B, a proteolytic enzyme often expressed in metastatic carcinoma, releasing the unmodified parent compound. Another exemplified prodrug is:



318275: C44 H53 N5 O10

SOURCE – Seattle Genetics.

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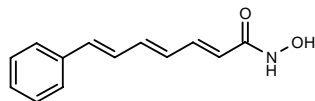
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CG-1521

317792

7-Phenyl-2,4,6-heptatrienhydroxamic acid



C13 H13 N O2; Mol wt: 215.2507

ACTION – Histone deacetylase inhibitor (IC_{50} = 1.8 μ M in rat liver) with strong antiproliferative activity in several cancer cell lines including prostate, breast and neuroblastoma cells (IC_{50} = 0.5-7.5 μ M). Compound produced a time- and concentration-dependent arrest in the G₂/M phase in breast cancer MCF-7 and prostate cancer LNCaP cells, and it also induced differentiation of these cell lines; apoptosis and downregulation of Bcl-2 were seen in both breast and prostate cancer cells. The maximum tolerated dose was 200 mg/kg/day i.p.; a dose of 100 mg/kg/day i.p. for 21 days reduced tumor volume in mice bearing human prostate PC-346C tumors. Pharmacokinetic experiments showed that compound was rapidly absorbed after p.o. or i.p. dosing and was rapidly cleared from plasma after i.v. administration, with a half-life of about 30 min.

SOURCE – CircaGen Pharmaceutical.

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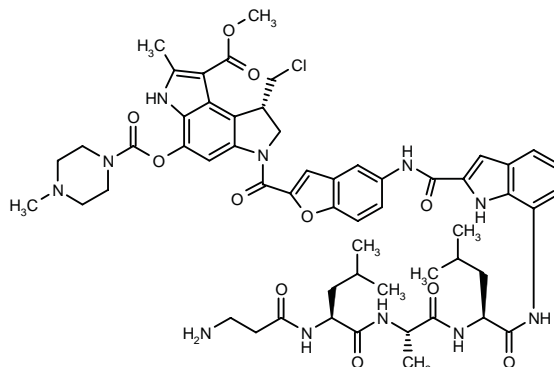
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CRX-103¹⁻⁴

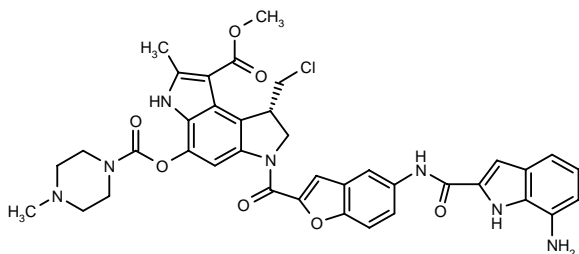
309985

β -Alanyl-L-leucyl-L-alanyl-L-leucine *N*-[2-[2-[1(*S*)-(chloromethyl)-8-(methoxycarbonyl)-7-methyl-5-(4-methylpiperazin-1-ylcarbonyloxy)-1,2,3,6-tetrahydrobenzo[1,2-*b*:4,3-*b'*]dipyrrol-3-ylcarbonyl]-1-benzofuran-5-ylcarbonyl]-1*H*-indol-7-yl]amide



C56 H68 Cl N11 O11; Mol wt: 1106.6720

ACTION – Antineoplastic agent, a conjugate of the duocarmycin analogue **CRX-395** with a tumor-activated prodrug (TAP) peptide that acts as a prodrug of CRX-395 and is relatively stable in plasma and inactive against tumor cells *in vitro*. The prodrug protected mice from the systemic toxicity of CRX-395, with maximum tolerated single i.v. doses of 5 and 1.5 mg/kg, respectively. In mouse xenograft models, the prodrug was well tolerated and highly effective in inhibiting tumor growth and prolonging survival in nude mice bearing doxorubicin-resistant human colorectal carcinoma HT-29, doxorubicin-resistant colorectal carcinoma LS 174T and doxorubicin-sensitive prostate carcinoma LNCaP tumors after single and multiple doses.



CRX-395 [310631]^{3,4}: C₃₈ H₃₆ Cl N₇ O₇

SOURCE – Corixa.

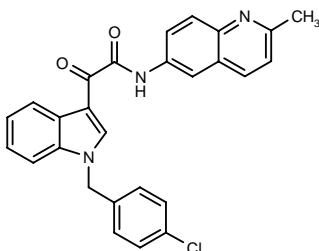
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D-69429

316800

2-[1-(4-Chlorobenzyl)-1*H*-indol-3-yl]-*N*-(2-methylquinolin-6-yl)-2-oxoacetamide



C₂₇ H₂₀ Cl N₃ O₂; Mol wt: 453.9270

ACTION – Antitumor agent displaying IC₅₀ values of 0.17, 0.17, 0.26 and 0.35 μM, respectively, against the cancer cell lines KB/HeLa (cervix), SK-OV-3 (ovarian), MCF-7 (breast) and L1210 (leukemia).

SOURCE – Zentaris.

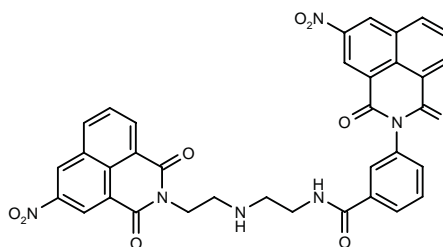
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DB-51630*

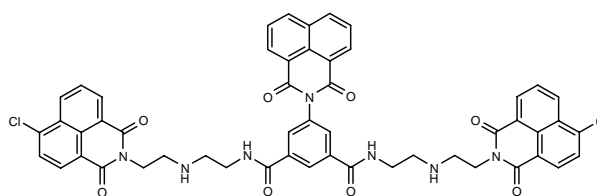
285295

3-(5-Nitro-1,3-dioxo-2,3-dihydro-1*H*-benzo[*de*]isoquinolin-2-yl)-*N*-[2-[2-(5-nitro-1,3-dioxo-2,3-dihydro-1*H*-benzo[*de*]isoquinolin-2-yl)ethylamino]ethyl]benzamide

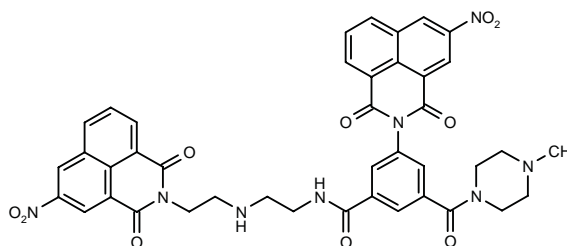


C₃₅ H₂₄ N₆ O₉; Mol wt: 672.6076

ACTION – Antineoplastic agent, a naphthalimidobenzamide derivative proven to induce p300, a transcriptional coactivator protein involved in many cell differentiation and signal transduction pathways. Compound exhibited strong antiproliferative activity against various cancer cell lines in the nanomolar range (IC₅₀ = 0.26 pM-64 nM) and it induced p300 mRNA at subnanomolar concentrations. For comparison, doxorubicin, vincristine, cisplatin, etoposide and actinomycin D did not increase p300 transcription. Potent *in vivo* antitumor activity was also seen against human solid tumor xenografts including human melanoma LOX (95% inhibition at 14.1 mg/kg i.v.) and human gastric cancer AZ-521 tumors (50% inhibition at 10 mg/kg i.v.). Other related compounds are:



DB-51808 [318194]: C₅₂ H₃₉ Cl₂ N₇ O₈



DB-51838 [318195]: C₄₁ H₃₆ N₈ O₁₀

SOURCE – Taiho.

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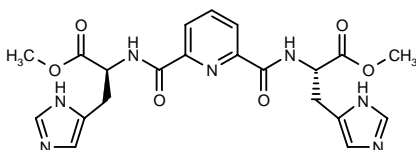
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*Identified compound **285295** (see **285293**) Drug Data Rep 2000, 022(04): 0374.

HPH-PEP

314338

N,N'-(Pyridin-2,6-diyl)bis(carbonyl)bis(L-histidine) dimethyl diester



C21 H23 N7 O6; Mol wt: 469.4557

ACTION – Synthetic peptide proven to sensitize leukemia cell lines to hyperthermia. It was not cytotoxic on its own, but in combination with hyperthermia (44 °C) it markedly reduced the survival of L1210, MOLT-4 and HL-60 cells. In particular, L1210 cells were highly sensitive, showing a survival rate of only 6.4% in the presence of heat and peptide at a concentration of 8.4 μM. Cell death induced by peptide under hyperthermic conditions did not appear to be apoptotic, but may involve peroxide formation.

SOURCES – Kumamoto University, Kumamoto (JP); Kyoto Prefectural University of Medicine, Kyoto (JP); Osaka Prefecture University, Osaka (JP).

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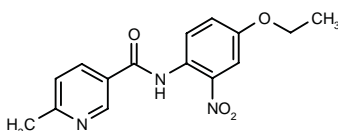
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MX-76629

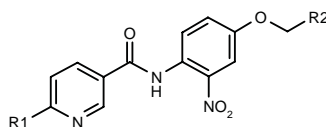
317988

N-(4-Ethoxy-2-nitrophenyl)-6-methylpyridine-3-carboxamide



C15 H15 N3 O4; Mol wt: 301.3005

ACTION – Apoptosis inducer, an *N*-phenylnicotinamide derivative active against cancer cells derived from a range of human solid tumors, with EC₅₀ values of 20-80 nM. Other related compounds are:



Compound	R1	R2	Formula
MX-56211 [310239]	Cl	Me	C ₁₄ H ₁₂ ClN ₃ O ₄
MX-55510 [317989]	Me	H	C ₁₄ H ₁₃ N ₃ O ₄

SOURCE – Maxim.

REFERENCES

1. Cai, S.X. and Drewe, J.A. (Cytovia, Inc.) *Substd. nicotinamides and analogs as activators of caspases and inducers of apoptosis and the use thereof.* WO 0155115.

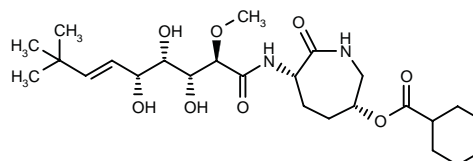
2. Cai, S.X. et al. *Discovery and optimization of substituted N-phenyl nicotinamides as potent apoptosis inducers using a cell and caspase based high throughput assay.* 223rd ACS Natl Meet (April 7-11, Orlando) 2002, Abst MEDI 198.

NVP-LAF-389*

290302

Cyclohexanecarboxylic acid 7-oxo-6(*S*)-[(2*R*,3*R*,4*S*,5*R*,6*E*)-3,4,5-trihydroxy-2-methoxy-8,8-dimethyl-6-nonenamido]perhydroazepin-3(*R*)-yl ester

LAF-389



C25 H42 N2 O8; Mol wt: 498.6128

ACTION – Synthetic analogue of the bengamides, a family of marine natural compounds isolated from a sponge, a methionine aminopeptidase inhibitor currently in phase I clinical trials for the treatment of solid tumors.

SOURCE – Novartis.

REFERENCES

1. Kinder, F.R. Jr. et al. (Novartis AG) *Certain substd. caprolactams, pharmaceutical compsns. containing them and a process for their preparation.* US 6239127.

2. Kinder, F.R. Jr. et al. (Novartis AG) *Certain substd. caprolactams, pharmaceutical compsns. containing them and their use in treating tumors.* EP 1131297, WO 0029382.

3. Dumez, H. et al. *Preliminary results of a phase I and pharmacokinetic study of LAF389 in patients with refractory solid tumors.* AACR-NCI-EORTC Int Conf Mol Targets Cancer Ther (Oct 29-Nov 2, Miami Beach) 2001, Abst 227.

4. Epstein, D. and Matter, A. *Oncology business unit: Poised to join the first tier.* Novartis R&D Invest Semin (Dec 6, Basel) 2000.

5. Kinder, F.R. Jr. et al. *Synthesis and antitumor activity of ester-modified analogues of bengamide B.* J Med Chem 2001, 44(22): 3692.

6. Phillips, P.E. et al. *A novel biomarker for methionine aminopeptidase inhibitors: NH2-terminal changes in 14-3-3? and detection in vitro and in vivo samples treated with NVP-LAF389*. Proc Amer Assoc Cancer Res 2002, 43: Abst 4732.

7. Reinhardt, J. *Innovation and productivity drive sustained growth*. Novartis R&D Invest Semin (Dec 6, Basel) 2000.

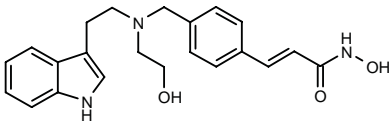
*Identified compound **290302** Drug Data Rep 2000, 022(09): 0843.

NVP-LAQ-824

310624

3-[4-[N-(2-Hydroxyethyl)-N-[2-(1*H*-indol-3-yl)ethyl]-aminomethyl]phenyl]-2-propenhydroxamic acid

LAQ-824



C22 H25 N3 O3; Mol wt: 379.4575

ACTION – Histone deacetylase (HDAC) inhibitor (IC₅₀ = 32 nM) able to transcriptionally activate the p21 promoter (EC₅₀ = 0.3 μM) and to inhibit the growth of human colon cancer HCT 116 cells (IC₅₀ = 10 nM), inducing cell cycle arrest in the G₂/M phase and promoting apoptosis. Compound also showed an IC₉₀ of < 0.1 μM against a panel of hematological tumor cells including primary acute myeloid leukemia, lymphoma and human and mouse leukemia cell lines. *In vivo*, it dose-dependently (5-100 mg/kg i.v.) inhibited the growth of established human colon cancer HCT 116, human lung cancer A549 and human breast cancer MDA-MB-435 xenografts in nude mice, with no related systemic toxicity. Compound is undergoing phase I clinical trials.

SOURCE – Novartis.

REFERENCES

1. Bair, K.W. et al. (Novartis AG; Novartis-Erfindungen VmbH) *Deacetylase inhibitors*. WO 0222577.

2. Atadja, P.W. et al. *In vitro and in vivo properties of LAQ824, a novel histone deacetylase inhibitor*. Proc Amer Assoc Cancer Res 2002, 43: Abst 347.

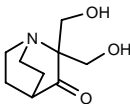
3. Perez, L.B. et al. *Discovery and SAR of NVP-LAQ824, a novel histone deacetylase inhibitor with in vitro and in vivo antitumor activity*. Proc Amer Assoc Cancer Res 2002, 43: Abst 3671.

4. *Novartis R&D day 2001: solid platform for sustained growth*. DailyDrugNews.com (Daily Essentials) 2001, Nov 7.

PRIMA-1

316471

2,2-Bis(hydroxymethyl)quinuclidin-3-one



C9 H15 N O3; Mol wt: 185.2215

ACTION – Antineoplastic agent proven to induce apoptosis and thereby suppress the growth of several tumor cell lines expressing mutant *p53* through restoration of the transcriptional transactivation function to mutant *p53*. Compound can restore the wild-type conformation and sequence-specific DNA-binding ability to mutant *p53* proteins. In mice bearing human tumor xenografts expressing mutant *p53*, compound significantly reduced tumor volume at a dose of 100 mg/kg i.p. or 20 mg/kg intratumorally.

SOURCES – Karolinska Institute, Stockholm (SE); Russian Academy of Sciences, Moscow (RU).

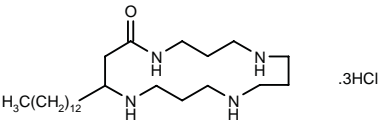
REFERENCES

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SL-1197

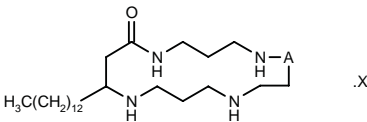
316819

4-Tridecyl-1,5,9,13-tetraazacyclohexadecan-2-one trihydrochloride



C25 H52 N4 O . 3HCl; Mol wt: 534.0955

ACTION – Agent with ATPase-like activity, potentially useful as an antitumor agent, particularly for the treatment of prostate cancer. It was shown to inhibit the growth of prostate cancer cells with ID₅₀ values of 0.58 (DuPro cells), 0.5 (PC-3 cells) and 2.60 μM (LNCaP cells). Other exemplified cyclic polyamine compounds are:



Compound	A	X	Formula
SL-11174 [316821]	-(CH2)2-	3HCl	C ₂₆ H ₅₄ N ₄ O.3HCl
SL-11199 [316824]	-(CH2)3-	3HCl	C ₂₇ H ₅₆ N ₄ O.3HCl
SL-11200 [316825]	-CH2NH(CH2)3-	4HCl	C ₂₈ H ₅₉ N ₅ O.4HCl

SOURCE – SLIL Biomedical.

REFERENCES

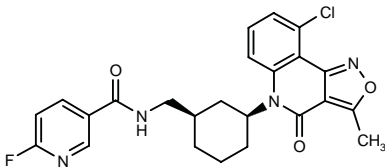
1. Frydman, B. et al. (SLIL Biomedical Corp.) *Cyclic polyamine cpds. for cancer therapy*. WO 0210142.

MODULATORS OF THE THERAPEUTIC
ACTIVITY OF
ANTINEOPLASTIC AGENTS

LY-487355

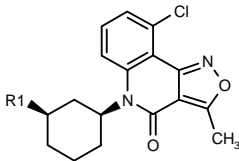
317931

N-[(1*R*,3*S*)-3-[9-Chloro-3-methyl-4-oxoisoxazolo[4,3-*c*]-quinolin-5(4*H*)-yl]cyclohexylmethyl]-6-fluoropyridine-3-carboxamide



C24 H22 Cl F N4 O3; Mol wt: 468.9138

ACTION – Multidrug resistance (MDR) modulator, an inhibitor of the MDR protein 1 (MRP1) with > 380-fold selectivity over P-glycoprotein. Compound completely reversed doxorubicin sensitivity in MRP1-transfected HeLa-T5 cells with EC₅₀ values of about 100 nM, and it also reversed navelbine and doxorubicin resistance in MRP1-overexpressing H69AR cells, but not parental H69 cells. In vesicles prepared from MRP1-transfected HeLa-T5 and MRP2-transfected HEK cells, it competitively inhibited MRP1-mediated LTC₄ uptake (K_i < 60 nM), but not MRP2-mediated LTC₄ uptake. *In vivo*, compound restored vincristine and navelbine sensitivity in the HeLa-T5 xenograft model and significantly increased the activity of doxorubicin in the MRP1-overexpressing NCI-H460 xenograft model. No toxicity or modification of vincristine plasma levels was seen in nude mice. Other related compounds are:



Compound	R1	Formula
LY-465803 [317929]	CH2NHCOPh	C ₂₅ H ₂₄ ClN ₃ O ₃
LY-509207 [317930]	(S)-4-F-PhCH(OH)CONH	C ₂₅ H ₂₃ ClFN ₃ O ₄

SOURCE – Lilly.

REFERENCES

1. Wang, Q. et al. (Eli Lilly and Company) *Methods and cpds. for inhibiting MRP1*. WO 0146199.

2. Dantzig, A.H. et al. *In vitro characterization of selective and highly potent tricyclic isoxazole inhibitors of multidrug resistance protein (MRP1)*. Proc Amer Assoc Cancer Res 2002, 43: Abst 4707.

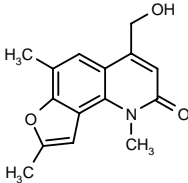
3. Law, K.L. et al. *In vivo reversal activity of potent tricyclic isoxazoles in MRP1 expressing xenograft models*. Proc Amer Assoc Cancer Res 2002, 43: Abst 4724.

RADIATION THERAPY

HOFQ

315953

4-Hydroxymethyl-1,6,8-trimethylfuro[2,3-*h*]quinolin-2(1*H*)-one



C15 H15 N O3; Mol wt: 257.2875

ACTION – Furoquinoline derivative, a photosensitizer with antiproliferative activity in Ehrlich ascites cells, which lost their ability to transmit the tumor by transplantation in mice. Moreover, compound strongly damaged both DNA and RNA synthesis *in vitro* without affecting protein synthesis. No mutagenicity or skin phototoxicity was seen.

SOURCE – Università degli Studi di Padova, Padova, (IT).

REFERENCES

1. Chiilin, A. et al. *Synthesis and biological evaluation of a new furo(2,3-h)quinolin-2(1H)-one*. J Med Chem 2002, 45(5): 1146.

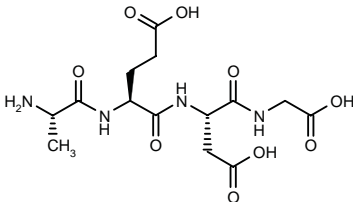
OCULAR MEDICATIONS

EPITALON

316689

L-Alanyl-L-glutamyl-L-aspartyl-glycine

Epithalon



C14 H22 N4 O9; Mol wt: 390.3468

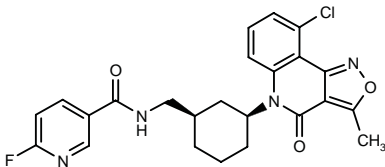
ACTION – Synthetic pineal tetrapeptide potentially useful for the treatment of retinitis pigmentosa. In rats with congenital retinitis pigmentosa, a single daily dose of 1 mg/kg injected into the parabulbar region of the eye for 72 days produced morphological and electrophysiological improvement by day 41 and prolonged retinal functional activity by 43.9%; significant retinal preservation was seen, and the time for complete destruction of the retinal layers was prolonged from 41 days (in control animals) to 72 days. In patients with pigmented retinal degeneration, compound stopped the development of pathology in 100% of cases and increased visual function in 80% of cases.

MODULATORS OF THE THERAPEUTIC
ACTIVITY OF
ANTINEOPLASTIC AGENTS

LY-487355

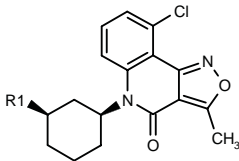
317931

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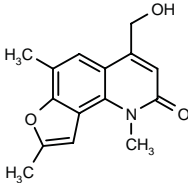
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RADIATION THERAPY

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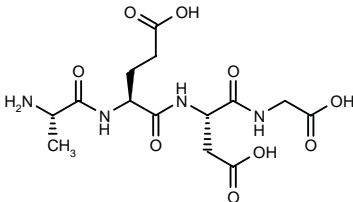
OCULAR MEDICATIONS

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316689

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SOURCE – Russian Academy of Medical Sciences, Moscow (RU).

REFERENCES

1. Khavinson, V.K. *Tetrapeptide revealing geroprotective effect, pharmacological substance on its basis, and the method of its application.* WO 0068255.

2. Anisimov, V.N. et al. *Effect of synthetic thymic and pineal peptides on biomarkers of ageing, survival and spontaneous tumour incidence in female CBA mice.* Mech Ageing Dev 2001, 122(1): 41.

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6. Khavinson, V. et al. *Synthetic tetrapeptide epitalon restores disturbed neuroendocrine regulation in senescent monkeys.* Neuroendocrinol Lett 2001, 22(4): 251.

7. Khavinson, V.K. *Role of peptide bioregulators in the mechanisms of ageing.* 2nd Eur Congr Biogerontol (Aug 25-28, St. Petersburg) 2000, Abst 34.

8. Khavinson, V.K. and Kvernoii, I.M. *Peptide bioregulators inhibit apoptosis.* Bull Exp Biol Med 2000, 130(12): 1175.

9. Khavinson, V.K. and Myl'nikov, S.V. *Effect of pineal tetrapeptide on antioxidant defense in Drosophila melanogaster.* Bull Exp Biol Med 2000, 129(4): 355.

10. Khavinson, V.K. et al. *Biological properties and therapeutic application of the synthetic pineal gland tetrapeptide.* 2nd Eur Congr Biogerontol (Aug 25-28, St. Petersburg) 2000, Abst 140.

11. Khavinson, V.K. et al. *Effect of epitalon on the lifespan increase in Drosophila melanogaster.* Mech Ageing Dev 2000, 120(1): 141.

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13. Khavinson, V.K. et al. *Regulating effect of epithalone on gastric endocrine cells in pinealectomized rats.* Bull Exp Biol Med 2000, 130(12): 1169.

14. Khavinson, V.K. et al. *Reparative effect of epithalon on pineal gland ultrastructure in gamma-irradiated rats.* Bull Exp Biol Med 2001, 131(1): 81.

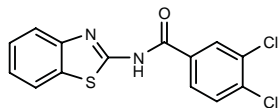
15. Khavinson, V.K.H. et al. *Effects of pineal peptides on neuroendocrine system after pinealectomy.* Arh Patol 2001, 63(3): 18.

METABOLIC DRUGS

TREATMENT OF BONE DISEASES

316246

N-(2-Benzothiazolyl)-3,4-dichlorobenzamide



C14 H8 Cl2 N2 O S; Mol wt: 323.2022

ACTION – Agent for the treatment of conditions associated with undesirable levels of bone resorption or deficiency in bone growth replacement, shown to increase alkaline phosphatase levels in mouse clonal chondrogenic TMC-23 cells by 2.5-fold compared to controls at 1 nM. Potentially useful for the treatment of osteoporosis, bone fracture or deficiency, primary or secondary hyperparathyroidism, periodontal disease, metastatic bone disease, osteolytic bone disease, postplastic surgery, postprosthetic joint surgery and postdental implantation.

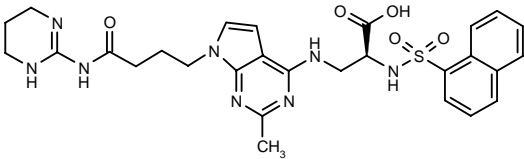
SOURCES – OsteoScreen; ZymoGenetics.

REFERENCES

1. Petrie, C. et al. (ZymoGenetics, Inc.;OsteoScreen, Inc.) *Comspns. and methods for treating bone deficit conditions.* US 6342514.

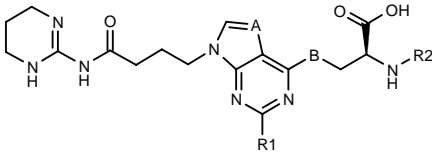
316315

3-[2-Methyl-7-[3-[N-(1,4,5,6-tetrahydropyrimidin-2-yl)carbamoyl]propyl]-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino]-2(S)-(naphthalen-1-ylsulfonamido)propionic acid



C28 H32 N8 O5 S; Mol wt: 592.6778

ACTION – A vitronectin ($\alpha_v\beta_3$) receptor antagonist (IC_{50} = 2.2 nM) with the ability to inhibit cell adhesion, as well as bone resorption. Potentially useful for the treatment of osteoporosis, cancer, inflammation, cardiovascular disorders such as restenosis and arteriosclerosis, nephropathies, retinopathies, psoriasis and rheumatoid arthritis. Other exemplified guanidino derivatives are:



Compound	R1	R2	A	B	Formula
316319	H	CO2CH2Ph	N	NH	C ₂₄ H ₂₉ N ₉ O ₅
316320	Me	CO2CH2Ph	CH	NH	C ₂₆ H ₃₂ N ₉ O ₅
316322	Me	SO2Ph	CH	NH	C ₂₄ H ₃₀ N ₈ O ₅ S
316323	Me	4-Br-PhSO2	CH	NH	C ₂₄ H ₂₉ BrN ₈ O ₅ S
316324	Me	4-Br-PhSO2	CH	S	C ₂₄ H ₂₈ BrN ₇ O ₅ S ₂
316325	Me	1-Naph-SO2	CH	S	C ₂₆ H ₃₁ N ₇ O ₅ S ₂
316326	Me	SO2Ph	CH	S	C ₂₄ H ₂₉ N ₇ O ₅ S ₂

SOURCES – Aventis Pharma; Genentech.

REFERENCES

1. Peyman, A. et al. (Aventis Pharma Deutschland GmbH;Genentech, Inc.) *Novel guanidino derivs. as inhibitors of cell adhesion.* EP 1176145, WO 0210168.

SOURCE – Russian Academy of Medical Sciences, Moscow (RU).

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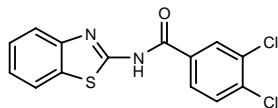
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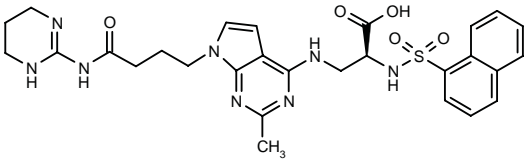
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REFERENCES

1. Petrie, C. et al. (ZymoGenetics, Inc.;OsteoScreen, Inc.) *Comspns. and methods for treating bone deficit conditions.* US 6342514.

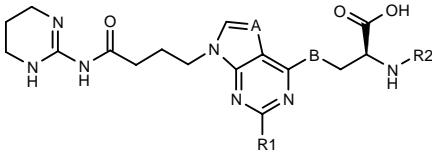
316315

3-[2-Methyl-7-[3-[N-(1,4,5,6-tetrahydropyrimidin-2-yl)carbamoyl]propyl]-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino]-2(S)-(naphthalen-1-ylsulfonamido)propionic acid



C28 H32 N8 O5 S; Mol wt: 592.6778

ACTION – A vitronectin ($\alpha_v\beta_3$) receptor antagonist (IC_{50} = 2.2 nM) with the ability to inhibit cell adhesion, as well as bone resorption. Potentially useful for the treatment of osteoporosis, cancer, inflammation, cardiovascular disorders such as restenosis and arteriosclerosis, nephropathies, retinopathies, psoriasis and rheumatoid arthritis. Other exemplified guanidino derivatives are:



Compound	R1	R2	A	B	Formula
316319	H	CO2CH2Ph	N	NH	C ₂₄ H ₂₉ N ₉ O ₅
316320	Me	CO2CH2Ph	CH	NH	C ₂₆ H ₃₂ N ₉ O ₅
316322	Me	SO2Ph	CH	NH	C ₂₄ H ₃₀ N ₈ O ₅ S
316323	Me	4-Br-PhSO2	CH	NH	C ₂₄ H ₂₉ BrN ₈ O ₅ S
316324	Me	4-Br-PhSO2	CH	S	C ₂₄ H ₂₈ BrN ₇ O ₅ S ₂
316325	Me	1-Naph-SO2	CH	S	C ₂₆ H ₃₁ N ₇ O ₅ S ₂
316326	Me	SO2Ph	CH	S	C ₂₄ H ₂₉ N ₇ O ₅ S ₂

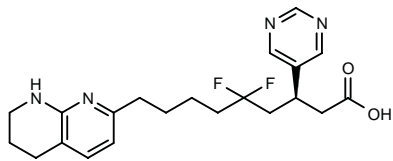
SOURCES – Aventis Pharma; Genentech.

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1. Peyman, A. et al. (Aventis Pharma Deutschland GmbH;Genentech, Inc.) *Novel guanidino derivs. as inhibitors of cell adhesion.* EP 1176145, WO 0210168.

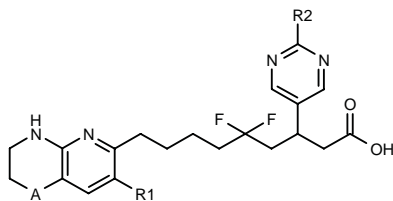
316506

5,5-Difluoro-3(*S*)-(5-pyrimidinyl)-9-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)nonanoic acid



C21 H26 F2 N4 O2; Mol wt: 404.4584

ACTION – Integrin α_v , $\alpha_v\beta_3$ and/or $\alpha_v\beta_5$ receptor antagonist, potentially useful for the treatment of osteoporosis and cancer, as well as restenosis, angiogenesis, diabetic retinopathy, macular degeneration, inflammation, arthritis and viral infections. Other specifically claimed compounds are:



Compound	R1	R2	A	Isomer	Formula
316507	H	H	CH2	R	C ₂₁ H ₂₆ F ₂ N ₄ O ₂
316508	H	OMe	CH2	R	C ₂₂ H ₂₈ F ₂ N ₄ O ₃
316509	H	OMe	CH2	S	C ₂₂ H ₂₈ F ₂ N ₄ O ₃
316510	H	Me	CH2	R	C ₂₂ H ₂₈ F ₂ N ₄ O ₂
316511	H	Me	CH2	S	C ₂₂ H ₂₈ F ₂ N ₄ O ₂
316512	cyclopropyl	Me	CH2	S	C ₂₅ H ₃₂ F ₂ N ₄ O ₂
316513	cyclopropyl	Me	CH2	R	C ₂₅ H ₃₂ F ₂ N ₄ O ₂
316514	H	H	CH2CH2	S	C ₂₂ H ₂₈ F ₂ N ₄ O ₂
316515	H	H	CH2CH2	R	C ₂₂ H ₂₈ F ₂ N ₄ O ₂
316516	H	Me	CH2CH2	S	C ₂₃ H ₃₀ F ₂ N ₄ O ₂
316517	H	Me	CH2CH2	R	C ₂₃ H ₃₀ F ₂ N ₄ O ₂
316518	H	OMe	CH2CH2	S	C ₂₃ H ₃₀ F ₂ N ₄ O ₃
316519	H	OMe	CH2CH2	R	C ₂₃ H ₃₀ F ₂ N ₄ O ₃

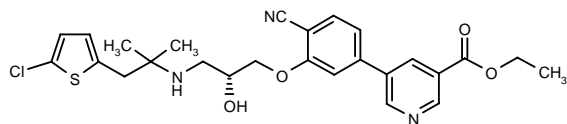
SOURCE – Merck & Co.

REFERENCES

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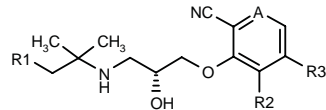
316575

5-[3-[3-[2-(5-Chlorothien-2-yl)-1,1-dimethylethylamino]-2(*R*)-hydroxypropoxy]-4-cyanophenyl]pyridine-3-carboxylic acid ethyl ester



C26 H28 Cl N3 O4 S; Mol wt: 514.0432

ACTION – Calcium receptor antagonist (calcilytic) expected to be useful for the treatment of diseases caused by abnormal bone or mineral homeostasis such as hypoparathyroidism, osteosarcoma, periodontal disease, arthritis, Paget’s disease, humoral hypercalcemia of malignancy and osteoporosis. Preferably, it is coadministered with an antiresorptive agent. Other specifically claimed compounds are:



Compound	R1	R2	R3	A	Formula
316577	2-indanyl	H	5-(CO2Et)-3-Pyr	CH	C ₃₁ H ₃₅ N ₃ O ₄
316580	4-MeO-Ph	H	5-(CO2Et)-3-Pyr	CH	C ₂₉ H ₃₃ N ₃ O ₅
316581	5-Cl-2-thienyl	H	3-(CO2Et)-2-Pyr	CH	C ₂₈ H ₂₈ ClN ₃ O ₄ S
316582	2-indanyl	H	3-(CO2Et)-2-Pyr	CH	C ₃₁ H ₃₅ N ₃ O ₄
316583	4-MeO-Ph	H	3-(CO2Et)-2-Pyr	CH	C ₂₉ H ₃₃ N ₃ O ₅
316584	5-Cl-2-thienyl	4-(CO2Et)-Ph	H	N	C ₂₆ H ₂₈ ClN ₃ O ₄ S
316585	2-indanyl	4-CO2H-Ph	H	N	C ₂₉ H ₃₁ N ₃ O ₄
316586	4-MeO-Ph	4-CO2H-Ph	H	N	C ₂₇ H ₂₉ N ₃ O ₅

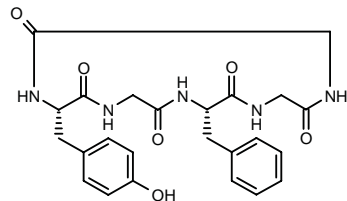
SOURCE – GlaxoSmithKline.

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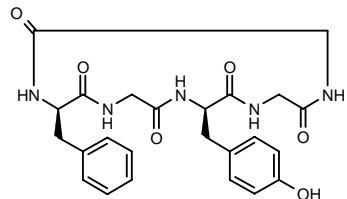
317913

Cyclo(L-tyrosyl-glycyl-L-phenylalanyl-glycyl-glycine)



C24 H27 N5 O6; Mol wt: 481.5063

ACTION – Cyclostereoisomer of the osteogenic growth peptide (OGP) C-terminal pentapeptide OGP(10-14) with superior proliferative activity compared to the parent compound in osteoblastic MC3T3 E1 cells. Potentially useful for the treatment of osteoporosis. Another related compound is:



317914: C24 H27 N5 O6

SOURCES – Hebrew University, Jerusalem (IL); Yissum.

REFERENCES

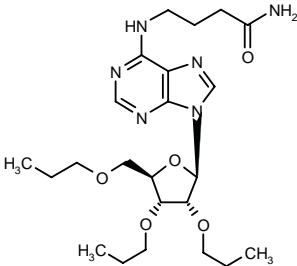
1. Bab, I. et al. (Yissum Research Development Co.) *Synthetic peptides and pseudopeptides having osteogenic activity and pharmaceutical compsns. containing the same*. JP 2000507925, WO 9732594.

2. Chen, Y.-C. et al. *Bioactive pseudopeptidic analogues and cyclostereoisomers of osteogenic growth peptide C-terminal pentapeptide, OGP(10-14)*. J Med Chem 2002, 45(8): 1624.

TREATMENT OF LIPOPROTEIN DISORDERS

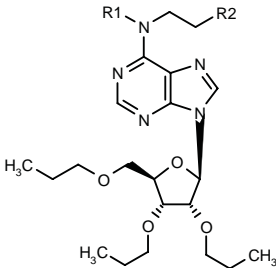
315590

N⁶-(3-Carbamoylpropyl)-2',3',5'-tri-*O*-propyladenosine



C23 H38 N6 O5; Mol wt: 478.5902

ACTION – Antihyperlipidemic shown to reduce serum triglyceride levels in normal rats and Triton WR-1339-loaded rats (hypertriglyceridemia model) by 33 and 43%, respectively, following oral administration at 1 mg/ml/100 g body weight. Other exemplified adenosine derivatives include the following:



Compound	R1	R2	Formula
315592	H	CONH2	C ₂₂ H ₃₆ N ₆ O ₅
315593	H	CH2CH2CONH2	C ₂₄ H ₄₀ N ₆ O ₅
315594	Me	CH2CONH2	C ₂₄ H ₄₀ N ₆ O ₅
315595	H	Et	C ₂₃ H ₃₉ N ₆ O ₄
315596	H	1-Pip-COCH2	C ₂₈ H ₄₆ N ₆ O ₅
315704	H	4-morpholinyl-COCH2	C ₂₇ H ₄₄ N ₆ O ₆

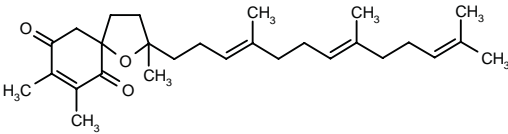
SOURCE – Nikken Chemicals.

REFERENCES

1. Wermuth, C.-G. et al. (Nikken Chemicals Co., Ltd.) *Adenosine cpd. and pharmaceutical compsn. containing the same*. WO 0204474.

316088

2,7,8-Trimethyl-2-(4,8,12-trimethyl-3,7,11-tridecatrienyl)-1-oxaspiro[4.5]dec-7-ene-6,9-dione



C28 H42 O3; Mol wt: 426.6368

ACTION – A representative compound from a series of tocotrienolquinone derivatives for use in the treatment of diseases associated with hypercholesterolemia such as arteriosclerosis, thrombosis and heart failure, as well as in the treatment of cancer.

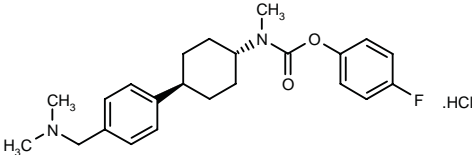
SOURCE – BASF (Abbott).

REFERENCES

1. Baldenius, K.-U. et al. (BASF AG) *Tocotrienolquinone cyclisation product with an anti-hypercholesterol effect*. DE 10034233, WO 0206261.

316469

trans-*N*-[4-[4-(Dimethylaminomethyl)phenyl]cyclohexyl]-*N*-methylcarbamic acid 4-fluorophenyl ester hydrochloride



C23 H29 F N2 O2 . HCl; Mol wt: 420.9530

ACTION – A representative compound from a series of carbamic and thiocarbamic acid derivatives with the ability to inhibit the biosynthesis of cholesterol via inhibition of 2,3-epoxysqualene-lanosterol cyclase (lanosterol synthase). Compound was shown to inhibit the incorporation of [¹⁴C]-acetate into steroids *in vitro* with an IC₅₀ of 0.5 nM. It also demonstrated *in vivo* activity, inducing accumulation of 2,3-epoxysqualene in the liver following oral administration to rats, and displaying cholesterol-, β-lipoprotein cholesterol- and HDL cholesterol-lowering activity in normolipemic hamsters at a dose of 1.73 mg/kg/day. Compound also displayed *in vitro* activity against a panel of fungal strains. Potentially useful for the treatment of hypercholesterolemia, hyperlipoproteinemia and hypertriglyceridemia, as well as diseases related therewith including coronary heart disease, cerebral ischemia, intermittent claudication, gangrene, gallstones and mycoses.

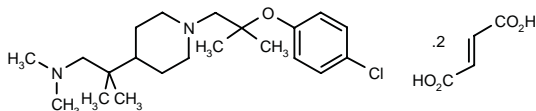
SOURCE – Boehringer Ingelheim.

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1. Maier, R. et al. (Boehringer Ingelheim Pharma KG) *Urethanes, thio and dithio analogues and their use as inhibitors of cholesterol biosynthesis*. DE 19754795, US 6346545, WO 9929662.

317203

N-[2-[1-[2-(4-Chlorophenoxy)-2-methylpropyl]piperidin-4-yl]-2-methylpropyl]-*N,N*-dimethylamine difumarate



C21 H35 Cl N2 O . 2 C4 H4 O4; Mol wt: 599.1167

ACTION – 2,3-Oxidosqualene cyclase (lanosterol synthase) inhibitor ($IC_{50} = 0.018 \mu M$), potentially useful as a hypocholesterolemic agent for the prevention of cardiovascular diseases.

SOURCE – Fournier.

REFERENCES

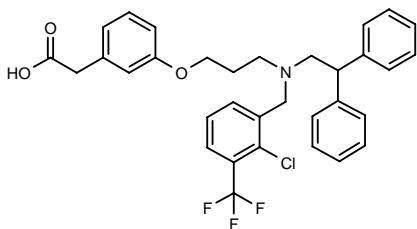
1. Binet, J. et al. (Laboratoires Fournier SA) *Derivs. of β,β -dimethyl-4-piperidineethanamine as inhibitors of the cholesterol biosynthesis*. EP 0699187, FR 2705343, JP 1996510726, US 5614534, WO 9426713.

2. Binet, J. et al. *Structure activity relationships of new inhibitors of mammalian 2,3-oxidosqualene cyclase designed from isoquinoline derivatives*. Chem Pharm Bull 2002, 50(3): 316.

GW-3965

317876

2-[3-[3-[*N*-[2-Chloro-3-(trifluoromethyl)benzyl]-*N*-(2,2-diphenylethyl)amino]propoxy]phenyl]acetic acid



C33 H31 Cl F3 N O3; Mol wt: 582.0589

ACTION – Potent and selective nonsteroidal liver X receptor (LXR) agonist proven to promote cholesterol efflux to apolipoprotein A-I (apo A-I) via an increase in mRNA of both *ABCA1* and *ABC8* genes. Potentially useful for the treatment of lipoprotein disorders.

SOURCE – GlaxoSmithKline.

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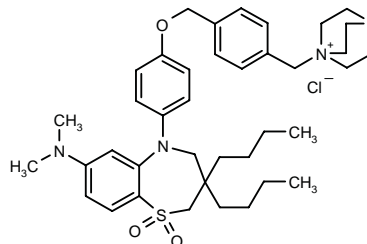
2. Collins, J.L. et al. *Identification of a non-steroidal LXR agonist through parallel array synthesis of tertiary amines*. 223rd ACS Natl Meet (April 7-11, Orlando) 2002, Abst MEDI 123.

3. Collins, J.L. et al. *Identification of a nonsteroidal liver X receptor agonist through parallel array synthesis of tertiary amines*. J Med Chem 2002, 45(10): 1963.

PHA-384640E

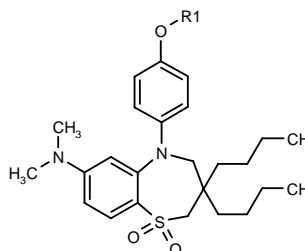
316391

1-[4-[4-[3,3-Dibutyl-7-(dimethylamino)-1,1-dioxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-5-yl]phenoxymethyl]-benzyl]-4-aza-1-azoniabicyclo[2.2.2]octane chlroride

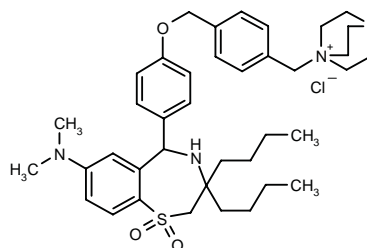


C39 H55 Cl N4 O3 S; Mol wt: 695.4075

ACTION – Antihyperlipidemic agent, an ileal bile acid transporter (IBAT) inhibitor proven to inhibit [^{14}C]-taurocholate uptake in BHK cells expressing human IBAT with an IC_{50} of $0.031 \mu M$. Particularly useful for the treatment of atherosclerosis. Other exemplified benzothiazepine compounds are:



Compound	R1	Formula
316393	H	C ₂₅ H ₃₆ N ₂ O ₃ S
316395	Me	C ₂₆ H ₃₈ N ₂ O ₃ S



316394: C39 H55 Cl N4 O3 S

SOURCE – Pharmacia.

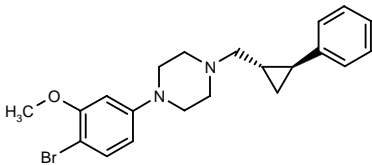
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TREATMENT OF OBESITY
AND NUTRITIONAL DISORDERS

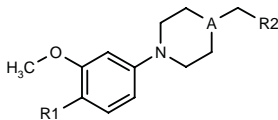
315889

trans-1-(4-Bromo-3-methoxyphenyl)-4-(2-phenylcyclopropylmethyl)piperazine



C21 H25 Br N2 O; Mol wt: 401.3455

ACTION – Modulator of the melanin-concentrating hormone type 1 (MCH1) receptor, potentially useful for the treatment of obesity. Other exemplified compounds are:



Compound	R1	R2	A	Formula
315891	I	<i>trans</i> -2-Ph-cyclopropyl	N	C ₂₁ H ₂₅ IN ₂ O
315892	Ph	<i>trans</i> -2-Ph-cyclopropyl	N	C ₂₇ H ₃₀ N ₂ O
315893	Br	<i>trans</i> -2-(4-MeO-Ph)-cyclopropyl	N	C ₂₂ H ₂₇ BrN ₂ O ₂
315894	CF ₃	<i>trans</i> -2-Ph-cyclopropyl	CH	C ₂₃ H ₂₆ F ₃ NO
315896	Br	CH=CHPh	N	C ₂₀ H ₂₃ BrN ₂ O
315897	Br	2-MeO-PhCH=CH	N	C ₂₁ H ₂₅ BrN ₂ O ₂
315898	Br	2,3-(MeO)2-PhCH=CH	N	C ₂₂ H ₂₇ BrN ₂ O ₃
315899	Br	2,4-(MeO)2-PhCH=CH	N	C ₂₂ H ₂₇ BrN ₂ O ₃

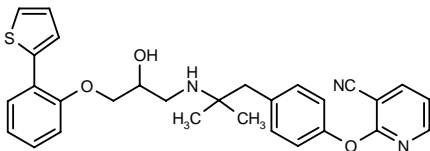
SOURCE – Neurogen.

REFERENCES

1. Bakthavatchalam, R. et al. (Neurogen Corp.) *Melanin concentrating hormone receptor ligands*. WO 0204433.

316108

2-[4-[2-[2-Hydroxy-3-[2-(2-thienyl)phenoxy]propylamino]-2-methylpropyl]phenoxy]pyridine-3-carbonitrile



C29 H29 N3 O3 S; Mol wt: 499.6321

ACTION – A specifically claimed compound from a series of β_3 -adrenoceptor agonists, particularly useful for the treatment of obesity and type 2 diabetes.

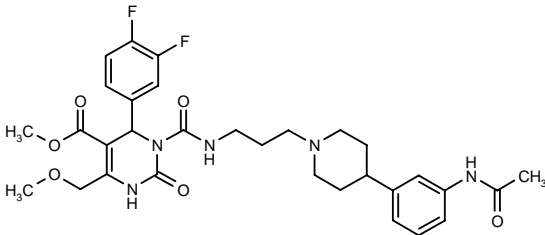
SOURCE – Lilly.

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1. Evers, B. et al. (Eli Lilly and Company) *β_3 Adrenergic agonists*. WO 0206276.

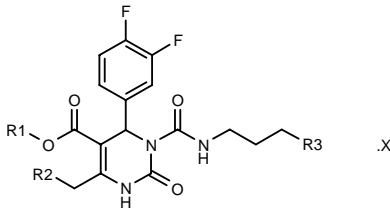
316172

(+)-3-[*N*-[3-[4-(3-Acetamidophenyl)piperidin-1-yl]propyl]-carbamoyl]-4-(3,4-difluorophenyl)-6-(methoxymethyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester

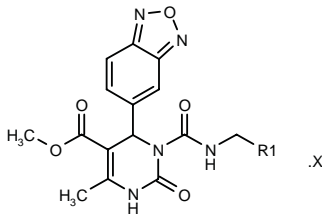


C31 H37 F2 N5 O6; Mol wt: 613.6583

ACTION – A melanin-concentrating hormone type 1 (MCH1) receptor antagonist, with a K_b of 0.3 nM against human MCH1 receptors. When tested against other receptors, compound exhibited 370-fold selectivity over 5-HT_{2C} receptors, and > 500,000-fold selectivity over neuropeptide Y (NPY) Y₁ and Y₂ receptors and galanin GAL1, GAL2 and GAL3 receptors. Potentially useful for the treatment of eating disorders such as bulimia and obesity, as well as depression and anxiety. Other exemplified compounds are:



Compound	R1	R2	R3	Isomer	X	Formula
316173	Me	OMe	4-[3-(AcNH)-Ph]-1-Pip	(-)		C ₃₁ H ₃₇ F ₂ N ₅ O ₆
316174	Me	OMe	4-[3-(AcNH)-Ph]-1,2,5,6-tetrahydro-1-Pyr			C ₃₁ H ₃₅ F ₂ N ₅ O ₆
316175	H	Me	1H,3H-spiro[isobenzofuran-1,4'-piperidin]-1'-yl		HCl	C ₂₉ H ₃₂ F ₂ N ₄ O ₅ .HCl
316177	Me	OMe	4-(1-Naph)-1-Pip	(+)		C ₃₃ H ₃₆ F ₂ N ₄ O ₅
316181	Me	OMe	4-(4-F-2-Me-Ph)-1-Pip	(+)		C ₃₀ H ₃₅ F ₃ N ₄ O ₅
316183	Me	H	1H,3H-spiro[isobenzofuran-1,4'-piperidin]-1'-yl			C ₂₉ H ₃₂ F ₂ N ₄ O ₅



Compound	R1	X	Formula
316176	1-[4-N(Bu)2-PhCH2]-4-Pip		C ₃₅ H ₄₇ N ₇ O ₅
316179	1H,3H-spiro[isobenzofuran-1,4'-piperidin]-1'-yl-CH2CH2	HCl	C ₂₉ H ₃₂ N ₆ O ₆ .HCl

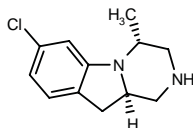
SOURCE – Synaptic.

REFERENCES

1. Lagu, B. et al. (Synaptic Pharmaceutical Corp.) *Selective melanin concentrating hormone-1 (MCH1) receptor antagonists and uses thereof*. WO 0206245.

316876

(4*R*,10*aR*)-7-Chloro-4-methyl-1,2,3,4,10,10*a*-hexahydro-pyrazino[1,2-*a*]indole



C12 H15 Cl N2; Mol wt: 222.7175

ACTION – 5-HT_{2C} receptor agonist with an EC₅₀ of 0.4 nM against human 5-HT_{2C} receptors expressed in CHO cells, and 47- and 8-fold selectivity, respectively, over 5-HT_{2A} and 5-HT_{2B} receptors. Potentially useful for the treatment of obesity, as well as a variety of CNS, cardiovascular and gastrointestinal disorders, particularly encephalitis, meningitis, thrombosis and gastrointestinal motility dysfunction.

SOURCES – Roche; Vernalis.

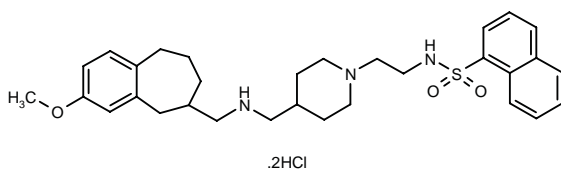
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FR-226928

307331

N-[2-[4-(3-Methoxy-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-6-yl)methylaminomethyl]piperidin-1-yl]ethyl]-naphthalene-1-sulfonamide dihydrochloride



C31 H41 N3 O3 S . 2HCl; Mol wt: 608.6707

ACTION – Potent neuropeptide Y (NPY) Y₅ receptor antagonist with nanomolar affinity for human Y₅ receptors (IC₅₀ = 16 nM) and good selectivity over Y₁ receptors (IC₅₀ = 9.6 μM). Potentially useful for the treatment of obesity.

SOURCE – Fujisawa.

REFERENCES

1. Sato, R. et al. (Fujisawa Pharmaceutical Co., Ltd.) *Organic sulfonamide cpds.* JP 2001172257.

2. Itani, H. et al. *Novel and potent neuropeptide Y-Y5 receptor antagonists: 1-Hydroxytetraline benzo[a]cycloheptene derivatives.* 21st Symp Med Chem (Nov 28-30, Kyoto) 2001, Abst 2P-36.

3. Itani, H. et al. *Novel potent antagonists of human neuropeptide Y Y5 receptors. Part 2: Substituted benzo[a]cycloheptene derivatives.* Bioorg Med Chem Lett 2002, 12(5): 757.

HEMATINIC AGENTS AND HEMATOPOIETIC GROWTH FACTORS

AF-15846 DIMER

316505

Bis[L-leucyl-L-leucyl-L-aspartyl-L-isoleucyl-L-cysteinyl-L-glutamyl-L-leucyl-L-lysyl-L-leucyl-L-glutamyl-L-glutamyl-L-cysteinyl-L-alanyl-L-arginyl-L-arginyl-L-cysteinyl-L-asparagine] *S*-3.5-*S*'-3.5':*S*-3.12-*S*'-3.12':*S*-3.16-*S*'-3.16'-tris(disulfide)

C166 H286 N52 O52 S6; Mol wt: 4034.7930

ACTION – A representative compound from a group of peptides with affinity for the granulocyte colony-stimulating factor receptor (G-CSFR). Potentially useful for enhancing leukocyte production in patients suffering from neutropenia associated with chemotherapy, AIDS and community-acquired pneumonia.

SOURCE – GlaxoSmithKline.

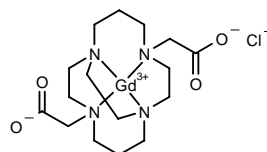
REFERENCES

1. Cwirla, S.E. et al. (GlaxoSmithKline plc) *Cpds. having affinity for the granulocyte-colony stimulating factor receptor (G-CSFR).* WO 0207676.

DIAGNOSTIC AGENTS

316135

[1,4,8,11-Tetraazabicyclo[6.6.2]hexadecan-4,11-di-acetato-κN¹,κN⁴,κN⁸,κN¹¹,κO⁴,κO¹¹]gadolinium chloride



C16 H28 Cl Gd N4 O4; Mol wt: 533.1242

ACTION – A macrocyclic compound based on the DOTA structure comprising a chelator and a paramagnetic metal ion, useful as a contrast agent for magnetic resonance imaging.

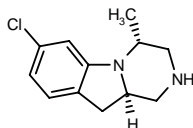
SOURCE – California Institute of Technology, Pasadena, CA (US).

REFERENCES

1. Hubin, T.J. and Meade, T.J. (California Institute of Technology) *Novel macrocyclic magnetic resonance imaging contrast agents.* WO 0206287.

316876

(4*R*,10*aR*)-7-Chloro-4-methyl-1,2,3,4,10,10*a*-hexahydro-pyrazino[1,2-*a*]indole



C12 H15 Cl N2; Mol wt: 222.7175

ACTION – 5-HT_{2C} receptor agonist with an EC₅₀ of 0.4 nM against human 5-HT_{2C} receptors expressed in CHO cells, and 47- and 8-fold selectivity, respectively, over 5-HT_{2A} and 5-HT_{2B} receptors. Potentially useful for the treatment of obesity, as well as a variety of CNS, cardiovascular and gastrointestinal disorders, particularly encephalitis, meningitis, thrombosis and gastrointestinal motility dysfunction.

SOURCES – Roche; Vernalis.

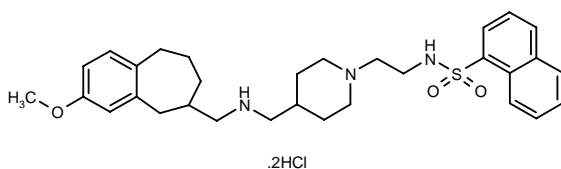
REFERENCES

1. Bentley, J.M. et al. (Vernalis Research Ltd.; F. Hoffmann-La Roche AG) *Piperazine derivs.* WO 0210169.

FR-226928

307331

N-[2-[4-(3-Methoxy-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-6-yl)methylaminomethyl]piperidin-1-yl]ethyl]-naphthalene-1-sulfonamide dihydrochloride



C31 H41 N3 O3 S . 2HCl; Mol wt: 608.6707

ACTION – Potent neuropeptide Y (NPY) Y₅ receptor antagonist with nanomolar affinity for human Y₅ receptors (IC₅₀ = 16 nM) and good selectivity over Y₁ receptors (IC₅₀ = 9.6 μM). Potentially useful for the treatment of obesity.

SOURCE – Fujisawa.

REFERENCES

1. Sato, R. et al. (Fujisawa Pharmaceutical Co., Ltd.) *Organic sulfonamide cpds.* JP 2001172257.

2. Itani, H. et al. *Novel and potent neuropeptide Y-Y5 receptor antagonists: 1-Hydroxytetraline benzo[a]cycloheptene derivatives.* 21st Symp Med Chem (Nov 28-30, Kyoto) 2001, Abst 2P-36.

3. Itani, H. et al. *Novel potent antagonists of human neuropeptide Y Y5 receptors. Part 2: Substituted benzo[a]cycloheptene derivatives.* Bioorg Med Chem Lett 2002, 12(5): 757.

HEMATINIC AGENTS AND HEMATOPOIETIC GROWTH FACTORS

AF-15846 DIMER

316505

Bis[L-leucyl-L-leucyl-L-aspartyl-L-isoleucyl-L-cysteinyl-L-glutamyl-L-leucyl-L-lysyl-L-leucyl-L-glutamyl-L-glutamyl-L-cysteinyl-L-alanyl-L-arginyl-L-arginyl-L-cysteinyl-L-asparagine] *S*-3.5-*S*'-3.5':*S*-3.12-*S*'-3.12':*S*-3.16-*S*'-3.16'-tris(disulfide)

C166 H286 N52 O52 S6; Mol wt: 4034.7930

ACTION – A representative compound from a group of peptides with affinity for the granulocyte colony-stimulating factor receptor (G-CSFR). Potentially useful for enhancing leukocyte production in patients suffering from neutropenia associated with chemotherapy, AIDS and community-acquired pneumonia.

SOURCE – GlaxoSmithKline.

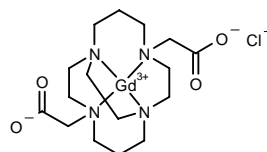
REFERENCES

1. Cwirla, S.E. et al. (GlaxoSmithKline plc) *Cpds. having affinity for the granulocyte-colony stimulating factor receptor (G-CSFR).* WO 0207676.

DIAGNOSTIC AGENTS

316135

[1,4,8,11-Tetraazabicyclo[6.6.2]hexadecan-4,11-di-acetato-κN¹,κN⁴,κN⁸,κN¹¹,κO⁴,κO¹¹]gadolinium chloride



C16 H28 Cl Gd N4 O4; Mol wt: 533.1242

ACTION – A macrocyclic compound based on the DOTA structure comprising a chelator and a paramagnetic metal ion, useful as a contrast agent for magnetic resonance imaging.

SOURCE – California Institute of Technology, Pasadena, CA (US).

REFERENCES

1. Hubin, T.J. and Meade, T.J. (California Institute of Technology) *Novel macrocyclic magnetic resonance imaging contrast agents.* WO 0206287.

Tc-99m-PEIMP

316340

Poly(ethyleneiminomethylphosphonic acid)technetium-99mTc complex

ACTION – A complex composed of a phosphonate-containing polymer and a radionuclide ion for use in the *in vivo* diagnosis of hepatic fibrosis or necrosis. The complex demonstrated favorable pharmacokinetic and biodistribution profiles when administered to dogs or rats with liver fibrosis. This polymer complex was also shown to be nontoxic and nonpyrogenic when administered i.v. to mice and rabbits.

SOURCE – BTG.

REFERENCES

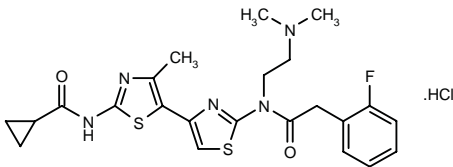
1. Milner, R.J. and Van der Merwe, S.W. (BTG International Ltd.) *Diagnosis of liver disease*. WO 0207782.

ANALGESIC AND ANESTHETIC
DRUGS

ANALGESIC DRUGS

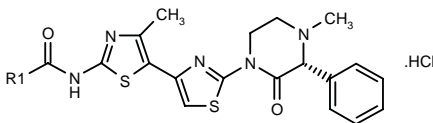
317734

N-[2-[*N*-[2-(Dimethylamino)ethyl]-2-(2-fluorophenyl)-acetamido]-4'-methyl-4,5'-bithiazol-2'-yl]cyclopropanecarboxamide hydrochloride

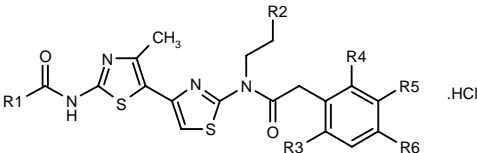


C23 H26 F N5 O2 S2 . HCl; Mol wt: 524.0823

ACTION – Protein kinase C γ (PKC γ) inhibitor (IC₅₀ = 0.0369 μ M) with > 20- and > 70-fold selectivity, respectively, relative to PKC α and PKC β II. *In vivo*, compound was effective in reducing licking in the formalin pain test when orally administered to rats at doses of 3 and 10 mg/kg. Potentially useful as an analgesic agent in the treatment of pain, hyperalgesia and allodynia, as well as in the treatment of narcotic analgesic resistance. Other exemplified thiazole compounds are:



Compound	R1	Formula
317735	cyclopropyl	C ₂₂ H ₂₃ N ₅ O ₂ S ₂ .HCl
317736	Me	C ₂₀ H ₂₁ N ₅ O ₂ S ₂ .HCl



Compound	R1	R2	R3	R4	R5	R6	Formula
317737	cyclopropyl	CH2N(Me)2	H	H	NHCOPh	H	C ₃₁ H ₃₄ N ₆ O ₃ S ₂ .HCl
317738	cyclopropyl	N(Me)2	H	H	NHCOPh	H	C ₃₀ H ₃₂ N ₆ O ₃ S ₂ .HCl
317739	cyclopropyl	N(Me)2	H	F	H	F	C ₂₃ H ₂₅ F ₂ N ₅ O ₂ S ₂ .HCl
317740	cyclopropyl	N(Me)2	F	F	H	H	C ₂₃ H ₂₅ F ₂ N ₅ O ₂ S ₂ .HCl
317741	Me	N(Me)2	H	F	H	H	C ₂₁ H ₂₄ FN ₅ O ₂ S ₂ .HCl
317742	cyclopropyl	N(Me)2	H	H	NHAc	H	C ₂₅ H ₃₀ N ₆ O ₃ S ₂ .HCl

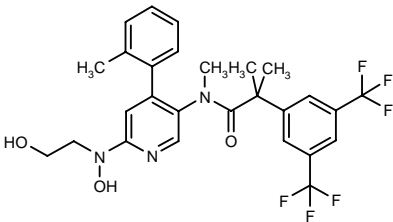
SOURCE – Japan Tobacco.

REFERENCES

1. Inaba, T. et al. (Japan Tobacco Inc.) *Thiazole cpds. and their medicinal use*. JP 2002053566.

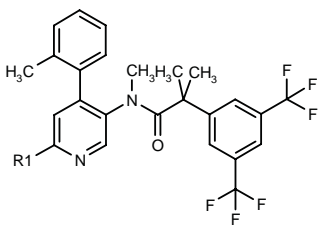
317962

2-[3,5-Bis(trifluoromethyl)phenyl]-*N*-[6-[*N*-hydroxy-*N*-(2-hydroxyethyl)amino]-4-(2-methylphenyl)pyridin-3-yl]-*N*,2-dimethylpropionamide

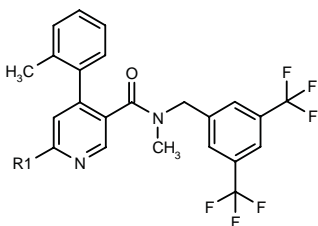


C27 H27 F6 N3 O3; Mol wt: 555.5163

ACTION – Tachykinin NK₁ receptor antagonist (pK_i = 9.28), expected to be useful for the treatment of pain, migraine, Alzheimer's disease, multiple sclerosis, morphine withdrawal, edema, rheumatoid arthritis, asthma, allergic rhinitis, ulcerative colitis, Crohn's disease, ocular injury and ocular inflammatory diseases, anxiety, depression, psychosis, motion sickness, urinary incontinence, etc. Other exemplified 4-phenylpyridine derivatives include the following:



Compound	R1	Formula
317963	NHCOCH2OH	C ₂₇ H ₂₅ F ₆ N ₃ O ₃
317964	2-(cyclopropyl-CONHCO)-cyclopropyl	C ₃₃ H ₃₁ F ₆ N ₃ O ₃
317965	Cl	C ₂₅ H ₂₁ ClF ₆ N ₂ O
317969	ethynyl	C ₂₇ H ₂₂ F ₆ N ₂ O



Compound	R1	Formula
317966	5-Ac-2-thienyl	C ₂₉ H ₂₂ F ₆ N ₂ O ₂ S
317967	1,2,3,6-tetrahydro-4-Pyr	C ₂₈ H ₂₅ F ₆ N ₃ O
317968	3-Me-1,2,4-oxadiazol-5-yl	C ₂₆ H ₂₀ F ₆ N ₄ O ₂
317970	2-Pyr-SO	C ₂₈ H ₂₁ F ₆ N ₃ O ₂ S
317971	O(CH2)3OH	C ₂₆ H ₂₄ F ₆ N ₂ O ₃

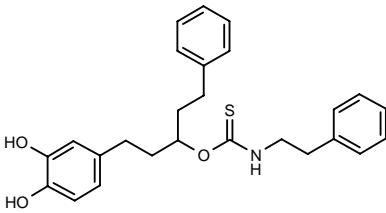
SOURCE – Roche.

REFERENCES

1. Godel, T. et al. (F. Hoffmann-La Roche AG) 4-Phenyl-pyridine derivs. as neurokinin-1 receptor antagonists. WO 0216324.

318060

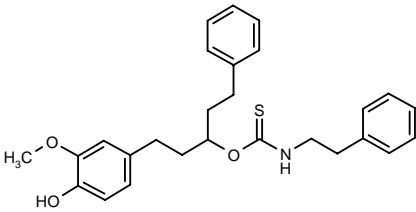
N-(2-Phenylethyl)thiocarbamic acid O-[3-(3,4-dihydroxyphenyl)-1-(2-phenylethyl)propyl] ester



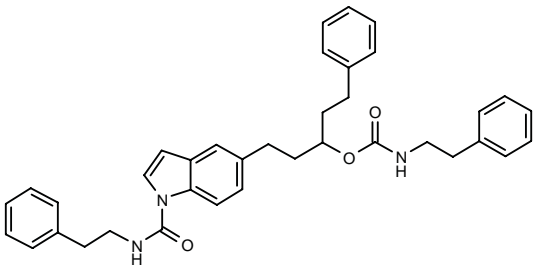
C26 H29 N O3 S; Mol wt: 435.5851

ACTION – Vanilloid receptor antagonist shown to prevent Ca²⁺ influx into neurons. Compound demonstrated *in vivo* activity in mouse models of analgesia and inflammation. In the mouse *p*-phenylquinone writhing test, it prevented writhing by 45% at 1 mg/kg i.p. It also reduced TPA-induced ear edema by 45% after topical administration at 1 mg/ear. Potentially useful for the treatment of acute and chronic pain (including neuropathic pain), migraine, arthralgia, nerve injury, diabetic and other neuropathies, neurodegenerative diseases, neurotic skin disorders, stroke, urinary bladder hypersensitivity, irritable bowel syndrome, inflammatory bowel disease, gastric or

duodenal ulcer, asthma, chronic obstructive pulmonary disease, and irritation of the skin, eyes and mucus membranes. Other exemplified thiocarbamic acid derivatives are:



318061: C27 H31 N O3 S



318062: C37 H39 N3 O3

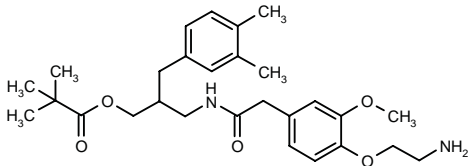
SOURCE – Pacific Corp.

REFERENCES

1. Suh, Y.G. et al. (Pacific Corp.) Novel thiocarbamic acid derivs. and the pharmaceutical compsns. containing the same. WO 0216317.

318547

2,2-Dimethylpropionic acid 3-[2-[4-(2-aminoethoxy)-3-methoxyphenyl]acetamido]-2-(3,4-dimethylbenzyl)propyl ester



C28 H40 N2 O5; Mol wt: 484.6330

ACTION – Vanilloid receptor agonist (EC₅₀ = 1.57 μM in the calcium influx assay) with potent analgesic activity against phenylbenzoquinone- and acetic acid-induced writhing in mice (ED₅₀ = 3.5 and 0.96 μg/kg, respectively). Selected as a candidate for further development as a potential analgesic.

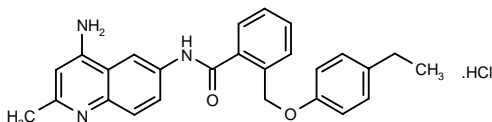
SOURCES – National Cancer Institute, Bethesda, MD (US); Pacific R&D Center (Pacific Corp.); Seoul National University, Seoul (KR).

REFERENCES

1. Lee, J. et al. Phenolic modification as an approach to improve the pharmacology of the 3-acyloxy-2-benzylpropyl homovanillic amides and thioureas, a promising class of vanilloid receptor agonists and analgesics. Bioorg Med Chem 2002, 10(4): 1171.

JTC-801***297035**

N-(4-Amino-2-methylquinolin-6-yl)-2-(4-ethylphenoxy-methyl)benzamide hydrochloride

C₂₆ H₂₅ N₃ O₂ . HCl; Mol wt: 447.9634

ACTION – Opioid receptor-like 1 (ORL1-N/OFQ) receptor antagonist (IC₅₀ = 2.58 μM for reversing nociceptin inhibition of forskolin-induced accumulation of cAMP in human ORL1 receptor-expressing HeLa cells) with nanomolar affinity for human receptors (IC₅₀ = 94 nM, K_i = 44 nM) and high selectivity over mu, delta and kappa opioid receptors. Compound exhibited antinociceptive activity in several acute pain models including noxious thermal and inflammatory pain models; it was effective against nociceptin-induced allodynia in mice (at 0.01 mg/kg i.v. and 1 mg/kg p.o. and above), reduced the first and second phase of the nociceptive response in the rat formalin test (MED = 0.01 mg/kg i.v. and 1 mg/kg p.o.) and prolonged the escape latency in the mouse hot-plate test (MED = 0.01 mg/kg i.v. and 1 mg/kg p.o.). The antinociceptive effect of compound could not be antagonized by naloxone, its potency and efficacy compared favorably to morphine, and it may be devoid of the dependence and tolerance associated with the opioid.

SOURCE – Japan Tobacco.

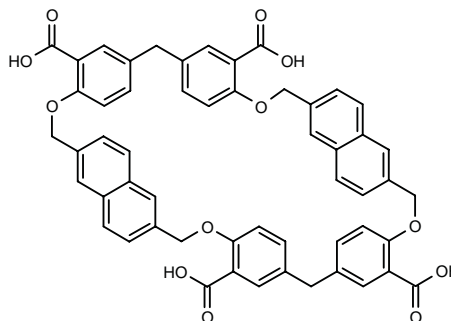
REFERENCES

1. Shinkai, H. et al. (Japan Tobacco Inc.) *Amide derivs. and nociceptin antagonists*. EP 1072263, JP 1999335355, WO 9948492.
2. Shinkai, H. et al. *4-Aminoquinolones: Novel nociceptin antagonists with analgesics activity*. J Med Chem 2000, 43(24): 4667.
3. Tulshian, D.B. *Survey of recent development in the SAR of the ORL-1 ligands & their potential therapeutic value*. 223rd ACS Natl Meet (April 7-11, Orlando) 2002, Abst MEDI 240.
4. Yamada, H. et al. *Pharmacological profiles of a novel opioid receptor-like1 (ORL1) receptor antagonist, JTC-801*. Br J Pharmacol 2002, 135(2): 323.
6. *Pharmaceuticals on clinical development*. Japan Tobacco Web Site 2001, Feb 7

*Identified compound **297035** Drug Data Rep 2001, 023(03): 0223.

ADJUNCTS TO ANESTHESIA**317285**

2,6-(Methanox[1,4]benzenomethano[1,4]benzenoxymethano[2,6]naphthalenomethanox[1,4]benzenomethano[1,4]benzenoxymethano)naphthalene-12,20,37,45-tetracarboxylic acid

C₅₄ H₄₀ O₁₂; Mol wt: 880.8980

ACTION – Cyclophane-based chelator of cationic muscle relaxant drugs, able to significantly reverse the neuromuscular block induced by pancuronium or gallamine in chick biventer muscle preparations with respective EC₅₀ values of 40 and 104 μM. Potentially useful as an adjunct to anesthesia.

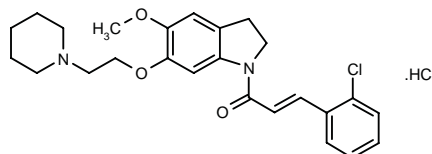
SOURCE – Organon.

REFERENCES

1. Bom, A.H.A. et al. (Akzo Nobel N.V.) *Use of chemical chelators as reversal agents for drug-induced neuromuscular block*. WO 0112202.
2. Cameron, K.S. et al. *Anionic cyclophanes as potential reversal agents of muscle relaxants by chemical chelation*. Bioorg Med Chem Lett 2002, 12(5): 753.

PSYCHOPHARMACOLOGIC DRUGS**ANXIOLYTICS****317477**

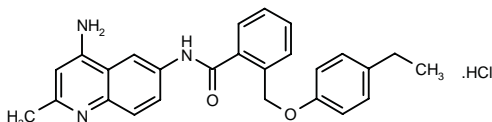
3-(2-Chlorophenyl)-1-[5-methoxy-6-[2-(1-piperidinyl)ethoxy]-2,3-dihydro-1*H*-indol-1-yl]-2(*E*)-propen-1-one hydrochloride

C₂₅ H₂₉ Cl N₂ O₃ . HCl; Mol wt: 477.4290

ACTION – 5-HT_{2C} receptor antagonist, potentially useful for the treatment of anxiety and depression. Other specifically claimed indoline derivatives are:

JTC-801***297035**

N-(4-Amino-2-methylquinolin-6-yl)-2-(4-ethylphenoxy-methyl)benzamide hydrochloride



C₂₆ H₂₅ N₃ O₂ . HCl; Mol wt: 447.9634

ACTION – Opioid receptor-like 1 (ORL1-N/OFQ) receptor antagonist (IC₅₀ = 2.58 μM for reversing nociceptin inhibition of forskolin-induced accumulation of cAMP in human ORL1 receptor-expressing HeLa cells) with nanomolar affinity for human receptors (IC₅₀ = 94 nM, K_i = 44 nM) and high selectivity over mu, delta and kappa opioid receptors. Compound exhibited antinociceptive activity in several acute pain models including noxious thermal and inflammatory pain models; it was effective against nociceptin-induced allodynia in mice (at 0.01 mg/kg i.v. and 1 mg/kg p.o. and above), reduced the first and second phase of the nociceptive response in the rat formalin test (MED = 0.01 mg/kg i.v. and 1 mg/kg p.o.) and prolonged the escape latency in the mouse hot-plate test (MED = 0.01 mg/kg i.v. and 1 mg/kg p.o.). The antinociceptive effect of compound could not be antagonized by naloxone, its potency and efficacy compared favorably to morphine, and it may be devoid of the dependence and tolerance associated with the opioid.

SOURCE – Japan Tobacco.

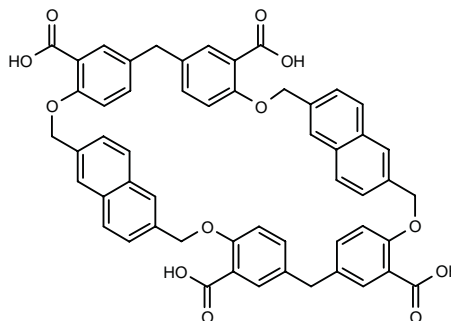
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*Identified compound **297035** Drug Data Rep 2001, 023(03): 0223.

ADJUNCTS TO ANESTHESIA**317285**

2,6-(Methanoxy[1,4]benzenomethano[1,4]benzenoxymethano[2,6]naphthalenomethanoxo[1,4]benzenomethano[1,4]benzenoxymethano)naphthalene-12,20,37,45-tetracarboxylic acid



C₅₄ H₄₀ O₁₂; Mol wt: 880.8980

ACTION – Cyclophane-based chelator of cationic muscle relaxant drugs, able to significantly reverse the neuromuscular block induced by pancuronium or gallamine in chick biventer muscle preparations with respective EC₅₀ values of 40 and 104 μM. Potentially useful as an adjunct to anesthesia.

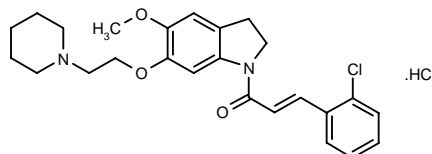
SOURCE – Organon.

REFERENCES

1. Bom, A.H.A. et al. (Akzo Nobel N.V.) *Use of chemical chelators as reversal agents for drug-induced neuromuscular block*. WO 0112202.
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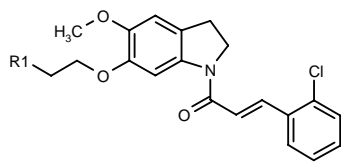
PSYCHOPHARMACOLOGIC DRUGS**ANXIOLYTICS****317477**

3-(2-Chlorophenyl)-1-[5-methoxy-6-[2-(1-piperidinyl)ethoxy]-2,3-dihydro-1*H*-indol-1-yl]-2(*E*)-propen-1-one hydrochloride



C₂₅ H₂₉ Cl N₂ O₃ . HCl; Mol wt: 477.4290

ACTION – 5-HT_{2C} receptor antagonist, potentially useful for the treatment of anxiety and depression. Other specifically claimed indoline derivatives are:



Compound	R1	Formula
317478	4-morpholinyl	C ₂₄ H ₂₇ ClN ₂ O ₄
317479	2-pyrrolidinyl	C ₂₄ H ₂₇ ClN ₂ O ₃
317480	2-oxa-5-azabicyclo[2.2.1]heptan-5-yl	C ₂₅ H ₂₇ ClN ₂ O ₄
317481	t-BuCH ₂ NH	C ₂₅ H ₃₁ ClN ₂ O ₃
317482	N(Et) ₂	C ₂₄ H ₂₉ ClN ₂ O ₃
317483	N(Me) ₂	C ₂₂ H ₂₅ ClN ₂ O ₃

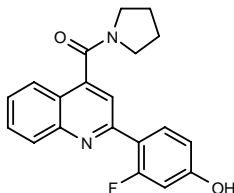
SOURCE – GlaxoSmithKline.

REFERENCES

1. Bromidge, S.M. et al. (GlaxoSmithKline plc) *Indoline derivs. as 5HT_{2C} antagonists*. WO 0214273.

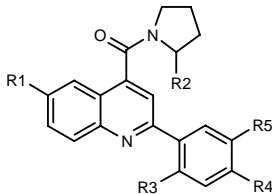
317767

1-[2-(2-Fluoro-4-hydroxyphenyl)quinolin-4-yl]-1-(1-pyrrolidinyl)methanone

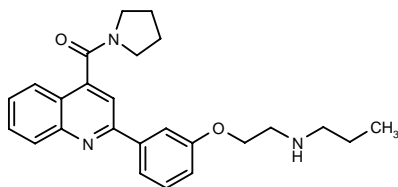


C₂₀ H₁₇ F N₂ O₂; Mol wt: 336.3643

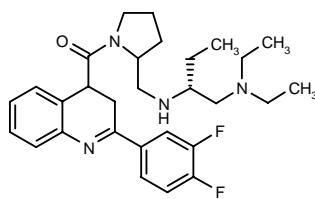
ACTION – Agent with high affinity for the benzodiazepine site of GABA_A receptors, considered to have potential in the treatment of CNS diseases, particularly anxiety, depression, sleep disorders and cognitive impairment. Other 2,4-disubstituted pyridine derivatives are:



Compound	R1	R2	R3	R4	R5	Isomer	Formula
317773	F	CH ₂ OH	H	F	F	R	C ₂₁ H ₁₇ F ₃ N ₂ O ₂
317776	F	CH ₂ OH	H	F	H	S	C ₂₁ H ₁₈ F ₂ N ₂ O ₂
317777	H	CH ₂ OH	F	OH	H	S	C ₂₁ H ₁₉ FN ₂ O ₃
317778	F	CH ₂ OH	H	F	H	racemic	C ₂₁ H ₁₈ F ₂ N ₂ O ₂
317779	H	CH ₂ OH	F	OH	H	racemic	C ₂₁ H ₁₉ FN ₂ O ₃
317780	H	CH ₂ NHCH ₂ CH ₂ N(Et) ₂	H	F	F	racemic	C ₂₇ H ₃₂ F ₂ N ₄ O



317771: C₂₅ H₂₉ N₃ O₂



317775: C₂₉ H₃₈ F₂ N₄ O

SOURCE – Neurogen.

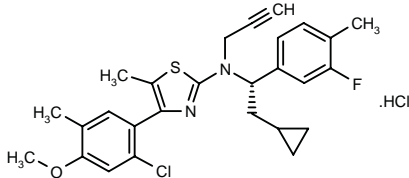
REFERENCES

1. Cai, G. et al. (Neurogen Corp.) *2,4-Substd. pyridine derivs*. WO 0214269.

SSR-125543A*

300361

4-(2-Chloro-4-methoxy-5-methylphenyl)-N-[2-cyclopropyl-1(S)-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-(2-propynyl)thiazol-2-amine hydrochloride



C₂₇ H₂₈ Cl F N₂ O S . HCl; Mol wt: 519.5091

ACTION – Potent, selective and orally active corticotropin-releasing factor CRF₁ receptor antagonist with high affinity for human cloned and native CRF₁ receptors (pK_i = 8.73 and 9.08, respectively) and high selectivity over the CRF_{2α} receptor and CRF-binding protein. Compound exhibited antagonist activity in *in vitro* functional tests; it antagonized CRF-induced cAMP synthesis in human retinoblastoma Y79 cells (IC₅₀ = 3.0 nM) and adrenocorticotropin hormone (ACTH) secretion in mouse pituitary tumor AtT-20 cells, while showing no agonist activity. In an *ex vivo* CRF₁ receptor binding assay in rats, compound inhibited the binding of [¹²⁵I-Tyr⁰]-ovine CRF in brain with an ID₅₀ value of 6.5 mg/kg p.o. and this effect lasted for over 24 h. It also produced long-lasting inhibition of the increase in plasma ACTH induced by i.c.v. CRF (ID₅₀ = 1, 5 and 5 mg/kg i.v., i.p. and p.o., respectively) or by restraint stress (73% at 10 mg/kg p.o.), and in gerbils it attenuated i.c.v. CRF-induced forepaw treading with an ID₅₀ of about 10 mg/kg p.o. Compound (3-30 mg/kg p.o. or i.p.) showed anxiolytic-like activity similar to the known CRF₁ receptor antagonist antalarmin in several rodent models of stress-related disorders including conflict procedures, the social defeat-induced anxiety model in mice and the defense test battery in mice. It also antagonized stress-induced hyperthermia, distress vocalization and cortical norepinephrine release, and exhibited antidepressant-like activity in the forced swimming test in rats at 30 mg/kg p.o. Furthermore, the dose of 10 mg/kg i.p. for 30 days significantly reversed the anxiogenic effects of chronic mild stress in mice. No significant side effects were seen in several tests for locomotor activity and memory in mice up to 100 mg. Potentially useful for the treatment of anxiety and depression.

SOURCE – Sanofi-Synthélabo.

REFERENCES

1. Fontaine, E. et al. (Sanofi-Synthélabo) *Aminothiazole derivs. and their use as CRF receptor ligands*. EP 1200419, FR 2796380, WO 0105776.

2. Griebel, G. et al. *4-(2-Chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]5-methyl-N-(2-propynyl)-1,3-thiazol-2-amine hydrochloride (SSR125543A): A potent and selective corticotrophin-releasing factor(1) receptor antagonist. II. Characterization in rodent models of stress-related disorders*. J Pharmacol Exp Ther 2002, 301(1): 333.

3. Gully, D. et al. *4-(2-Chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]5-methyl-N-(2-propynyl)-1,3-thiazol-2-amine hydrochloride (SSR125543A): A potent and selective corticotrophin-releasing factor(1) receptor antagonist. I. Biochemical and pharmacological characterization*. J Pharmacol Exp Ther 2002, 301(1): 322.

4. *Information Meeting*. Sanofi-Synthélabo Web Site 2001, Sept 3.

5. *R&D portfolio*. Sanofi-Synthélabo Web Site 2001, Aug 31.

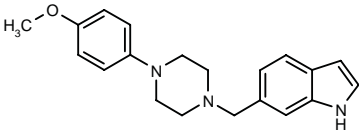
6. *R&D portfolio*. Sanofi-Synthélabo Web Site 2002, March 1.

*Identified compound **300361** (see **300356**) Drug Data Rep 2001, 023(06): 0535.

ANTIPSYCHOTIC DRUGS

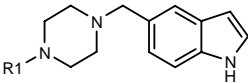
318019

6-[4-(4-Methoxyphenyl)piperazin-1-ylmethyl]-1*H*-indole

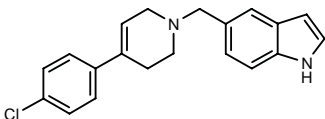


C20 H23 N3 O; Mol wt: 321.4217

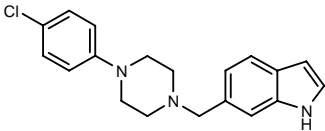
ACTION – Selective dopamine D4 ligand demonstrated to inhibit [³H]-YM-09151-2 binding to dopamine D4 receptors with an IC₅₀ of 9.1 nM, versus an IC₅₀ of > 10,000 nM against [³H]-spiperone binding to dopamine D2 receptors. Potentially useful for the treatment of psychosis, schizophrenia, cognitive disorders, attention deficit hyperactivity disorder and dyskinesia. Other exemplified indole derivatives are:



Compound	R1	Formula
318020	4-Cl-Ph	C ₁₉ H ₂₀ ClN ₃
318021	5-indolyl	C ₂₁ H ₂₂ N ₄
318022	4-MeO-Ph	C ₂₀ H ₂₃ N ₃ O
318023	Ph	C ₁₉ H ₂₁ N ₃



318024: C20 H19 Cl N2



318025: C19 H20 Cl N3

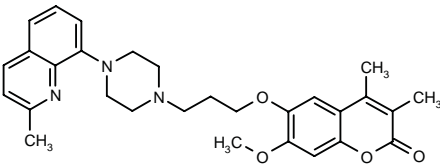
SOURCE – Lundbeck.

REFERENCES

1. Bang-Andersen, B. and Kehler, J. (H. Lundbeck A/S) *4-, 5-, 6-, and 7-indole derivs. useful for the treatment of CNS disorders*. WO 0216349.

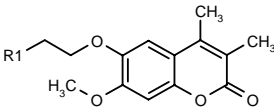
318036

7-Methoxy-3,4-dimethyl-6-[3-[4-(2-methylquinolin-8-yl)piperazin-1-yl]propoxy]-2*H*-1-benzopyran-2-one



C29 H33 N3 O4; Mol wt: 487.5967

ACTION – Dual-acting 5-HT_{1A} receptor agonist and dopamine D2 receptor antagonist, particularly useful for the treatment of schizophrenia. Other applications include Alzheimer's disease, hyperactivity disorders, disturbances in social behavior associated with mental retardation, depression, sexual dysfunction, sleep disorders, etc. Other specifically claimed chromenone derivatives are:



Compound	R1	Formula
318037	4-(4-indolyl)-1-Piz-CH2	C ₂₇ H ₃₁ N ₃ O ₄
318038	4-(8-quinoliny)-1-Piz-CH2	C ₂₈ H ₃₁ N ₃ O ₄
318039	4-(4-indolyl)-1-Piz	C ₂₆ H ₂₉ N ₃ O ₄
318040	4-(8-quinoliny)-1-Piz	C ₂₇ H ₂₉ N ₃ O ₄
318041	4-(2-Me-8-quinoliny)-1-Piz	C ₂₈ H ₃₁ N ₃ O ₄

SOURCE – Merck KGaA.

REFERENCES

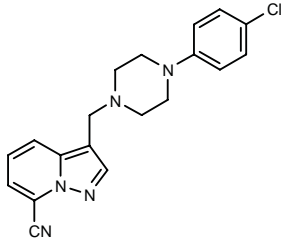
1. Gottschlich, R. et al. (Merck Patent GmbH) *Chromenone derivs. and their use for treating diseases in conjunction with 5-HT_{1A} receptors and/or dopamine D2 receptors*. DE 10041574, WO 0216354.

TREATMENT OF MOOD DISORDERS

FAUC-327

318578

3-[4-(4-Chlorophenyl)piperazin-1-ylmethyl]pyrazolo-[1,5-a]pyridine-7-carbonitrile



C19 H18 Cl N5; Mol wt: 351.8392

ACTION – High-affinity ligand for dopamine D4 receptors ($K_i = 1.5$ nM) with selectivity over D1, D2long, D2short and D3 receptors ($K_i = 2500, 44,000, 45,000$ and $26,000$ nM, respectively) and only moderate affinity for 5-HT_{1A} and 5-HT₂ receptors ($K_i = 2200$ and 180 nM, respectively). Compound exhibited potent partial agonist activity in CHO cells stably expressing the human D4.2 receptor, where it stimulated mitogenesis with an EC₅₀ of 1.5 nM and intrinsic activity of 31% relative to quinpirole. Potentially useful for the treatment of attention deficit hyperactivity disorder (ADHD), mood disorders and Parkinson's disease.

SOURCE – Friedrich-Alexander-Universität, Erlangen (DE).

REFERENCES

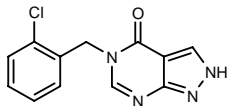
1. Löber, S. et al. Di- and trisubstituted pyrazolo[1,5-a]pyridine derivatives: Synthesis, dopamine receptor binding and ligand efficacy. Bioorg Med Chem Lett 2002, 12(4): 633.

NEUROLOGIC DRUGS

ANTIEPILEPTIC DRUGS

318142

5-(2-Chlorobenzyl)-4,5-dihydro-2H-pyrazolo[3,4-d]-pyrimidin-4-one



C12 H9 Cl N4 O; Mol wt: 260.6831

ACTION – Anticonvulsant reported to protect mice against convulsions induced by maximal electroshock (MES) and pentylenetetrazol following i.p. administration.

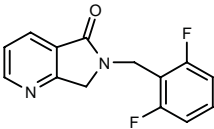
SOURCE – AWD.pharma (Pliva).

REFERENCES

1. Arnold, T. et al. (Arzneimittelwerk Dresden GmbH) 2,5-Dihydro-pyrazolo[3,4-d]-pyrimidin-4-ones with an anticonvulsive action and methods for producing the same. WO 0218387.

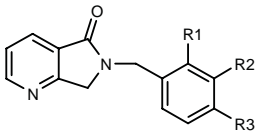
318144

6-(2,6-Difluorobenzyl)-6,7-dihydro-5H-pyrrolo[3,4-b]-pyridin-5-one



C14 H10 F2 N2 O; Mol wt: 260.2420

ACTION – Anticonvulsant with an oral ED₅₀ of 5.0 mg/kg in the rat maximal electroshock seizure (MES) test, shown to produce no neurotoxicity or tolerance in this animal model. It also exhibited protective effects in mice against convulsions induced by maximal electroshock and pentylenetetrazol following i.p. administration. Other exemplified compounds are:



Compound	R1	R2	R3	Formula
318145	H	H	Me	C ₁₅ H ₁₄ N ₂ O
318146	H	H	OMe	C ₁₅ H ₁₄ N ₂ O ₂
318147	H	H	Cl	C ₁₄ H ₁₁ ClN ₂ O
318148	H	Cl	H	C ₁₄ H ₁₁ ClN ₂ O
318149	Cl	H	H	C ₁₄ H ₁₁ ClN ₂ O
318150	H	H	F	C ₁₄ H ₁₁ FN ₂ O
318151	F	H	H	C ₁₄ H ₁₁ FN ₂ O
318153	CF3	H	H	C ₁₅ H ₁₁ F ₃ N ₂ O

SOURCE – AWD.pharma (Pliva).

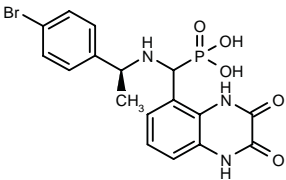
REFERENCES

1. Unverferth, K. et al. (Arzneimittelwerk Dresden GmbH) 6,7-Dihydro-pyrrolo[3,4-b]-pyridin-5-ones with an anticonvulsive action and methods for producing the same. DE 10042093, WO 0218381.

(1*RS*,1'*S*)-PEAQX

319238

1-[1(*S*)-(4-Bromophenyl)ethylamino]-1-(2,3-dioxo-1,2,3,4-tetrahydroquinoxalin-5-yl)methylphosphonic acid



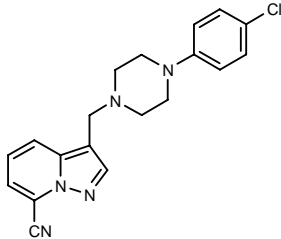
C17 H17 Br N3 O5 P; Mol wt: 454.2153

TREATMENT OF MOOD DISORDERS

FAUC-327

318578

3-[4-(4-Chlorophenyl)piperazin-1-ylmethyl]pyrazolo-[1,5-a]pyridine-7-carbonitrile



C19 H18 Cl N5; Mol wt: 351.8392

ACTION – High-affinity ligand for dopamine D4 receptors ($K_i = 1.5$ nM) with selectivity over D1, D2long, D2short and D3 receptors ($K_i = 2500, 44,000, 45,000$ and $26,000$ nM, respectively) and only moderate affinity for 5-HT_{1A} and 5-HT₂ receptors ($K_i = 2200$ and 180 nM, respectively). Compound exhibited potent partial agonist activity in CHO cells stably expressing the human D4.2 receptor, where it stimulated mitogenesis with an EC₅₀ of 1.5 nM and intrinsic activity of 31% relative to quinpirole. Potentially useful for the treatment of attention deficit hyperactivity disorder (ADHD), mood disorders and Parkinson's disease.

SOURCE – Friedrich-Alexander-Universität, Erlangen (DE).

REFERENCES

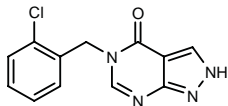
1. Löber, S. et al. Di- and trisubstituted pyrazolo[1,5-a]pyridine derivatives: Synthesis, dopamine receptor binding and ligand efficacy. Bioorg Med Chem Lett 2002, 12(4): 633.

NEUROLOGIC DRUGS

ANTIEPILEPTIC DRUGS

318142

5-(2-Chlorobenzyl)-4,5-dihydro-2H-pyrazolo[3,4-d]-pyrimidin-4-one



C12 H9 Cl N4 O; Mol wt: 260.6831

ACTION – Anticonvulsant reported to protect mice against convulsions induced by maximal electroshock (MES) and pentylenetetrazol following i.p. administration.

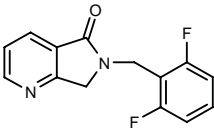
SOURCE – AWD.pharma (Pliva).

REFERENCES

1. Arnold, T. et al. (Arzneimittelwerk Dresden GmbH) 2,5-Dihydro-pyrazolo[3,4-d]-pyrimidin-4-ones with an anticonvulsive action and methods for producing the same. WO 0218387.

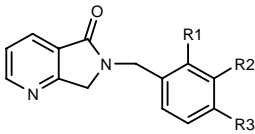
318144

6-(2,6-Difluorobenzyl)-6,7-dihydro-5H-pyrrolo[3,4-b]-pyridin-5-one



C14 H10 F2 N2 O; Mol wt: 260.2420

ACTION – Anticonvulsant with an oral ED₅₀ of 5.0 mg/kg in the rat maximal electroshock seizure (MES) test, shown to produce no neurotoxicity or tolerance in this animal model. It also exhibited protective effects in mice against convulsions induced by maximal electroshock and pentylenetetrazol following i.p. administration. Other exemplified compounds are:



Compound	R1	R2	R3	Formula
318145	H	H	Me	C ₁₅ H ₁₄ N ₂ O
318146	H	H	OMe	C ₁₅ H ₁₄ N ₂ O ₂
318147	H	H	Cl	C ₁₄ H ₁₁ ClN ₂ O
318148	H	Cl	H	C ₁₄ H ₁₁ ClN ₂ O
318149	Cl	H	H	C ₁₄ H ₁₁ ClN ₂ O
318150	H	H	F	C ₁₄ H ₁₁ FN ₂ O
318151	F	H	H	C ₁₄ H ₁₁ FN ₂ O
318153	CF3	H	H	C ₁₅ H ₁₁ F ₃ N ₂ O

SOURCE – AWD.pharma (Pliva).

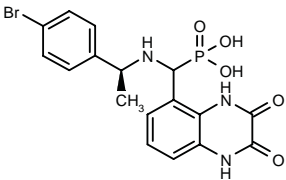
REFERENCES

1. Unverferth, K. et al. (Arzneimittelwerk Dresden GmbH) 6,7-Dihydro-pyrrolo[3,4-b]-pyridin-5-ones with an anticonvulsive action and methods for producing the same. DE 10042093, WO 0218381.

(1*RS*,1'*S*)-PEAQX

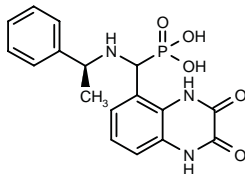
319238

1-[1(*S*)-(4-Bromophenyl)ethylamino]-1-(2,3-dioxo-1,2,3,4-tetrahydroquinoxalin-5-yl)methylphosphonic acid



C17 H17 Br N3 O5 P; Mol wt: 454.2153

ACTION – Potent and selective NMDA receptor antagonist with high binding affinity for the NMDA receptor (IC_{50} = 8 nM) and functional selectivity for NMDA 1A/2A over 1A/2B subunits (IC_{50} = 270 and 29,600 nM, respectively). *In vivo*, it protected mice against maximal electroshock (MES)-induced seizures with an ED_{50} value of 23 mg/kg i.p. Potentially useful as an anticonvulsant. Another related compound is:



319511: C17 H18 N3 O5 P

SOURCE – Novartis.

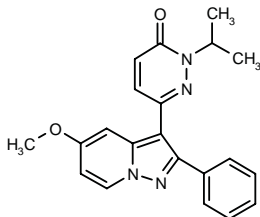
REFERENCES

1. Auberson, Y.P. et al. 5-Phosphonomethylquinoxalinediones as competitive NMDA receptor antagonist with a preference for the human 1A/2A, rather than 1A/2B receptor composition. Bioorg Med Chem Lett 2002, 12(7): 1099.

TREATMENT OF EXTRAPYRAMIDAL MOVEMENT DISORDERS

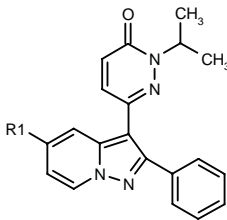
318130

2-Isopropyl-6-(5-methoxy-2-phenylpyrazolo[1,5-a]pyridin-3-yl)pyridazin-3(2H)-one



C21 H20 N4 O2; Mol wt: 360.4150

ACTION – A dual adenosine A_1 and A_2 (especially A_{2A}) receptor antagonist that displayed K_i values of 0.15 and 1.38 nM, respectively, against A_1 and A_{2A} receptors in binding assays. Potentially useful for the treatment of Parkinson's disease. Other applications include depression, dementia, anxiety, pain, cerebrovascular disease, heart failure, hypertension, circulatory insufficiency, bradyarrhythmia, multiple organ failure, renal diseases, edema, obesity, asthma, gout, hyperuricemia, sudden infant death syndrome, immunosuppression, diabetes, ulcer, pancreatitis, thrombosis, hypotension, constipation, angina pectoris and anemia, among others. Other exemplified pyrazolopyridine derivatives are:



Compound	R1	Formula
318131	OCH2CH2N(Me)2	C ₂₄ H ₂₇ N ₅ O ₂
318132	2-Pyr-O	C ₂₅ H ₂₁ N ₅ O ₂
318133	CON(Me)2	C ₂₃ H ₂₃ N ₅ O ₂
318134	4-Me-1-Piz	C ₂₅ H ₂₈ N ₆ O
318135	t-BuOCONH	C ₂₅ H ₂₇ N ₅ O ₃

SOURCE – Fujisawa.

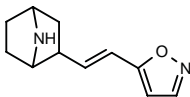
REFERENCES

1. Akahane, A. et al. (Fujisawa Pharmaceutical Co., Ltd.) Pyrazolopyridine cpd. and pharmaceutical use thereof. WO 0218382.

TREATMENT OF COGNITION DISORDERS

317131

2-[(E)-2-(5-Isoxazolyl)vinyl]-7-azabicyclo[2.2.1]heptane



C11 H14 N2 O; Mol wt: 190.2446

ACTION – Nicotinic acetylcholine receptor agonist (K_i = 80 nM) with potential in the treatment of pain, ulcerative colitis and CNS disorders including dementia, multiple cerebral infarctions, Parkinson's disease, Pick's disease, Huntington's chorea, tardive dyskinesia, hyperkinesia, mania, attention deficit disorder, anxiety, depression, mild cognitive impairment, dyslexia, schizophrenia and Tourette's syndrome, as well as in the treatment of syphilis and Creutzfeldt-Jakob disease.

SOURCE – Targacept.

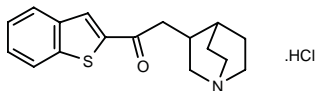
REFERENCES

1. Bhatti, B.S. and Clark, T.J. (Targacept, Inc.) Pharmaceutical compsns. and methods for use. WO 0212245.

317251

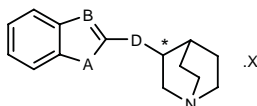
(+)-2-(1-Azabicyclo[2.2.2]oct-3-yl)-1-(1-benzothien-2-yl)ethanone hydrochloride

(+)-1-(1-Benzothien-2-yl)-2-(3-quinuclidinyl)ethanone hydrochloride

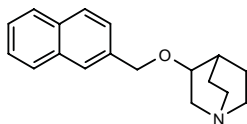


C₁₇ H₁₉ N O S . HCl; Mol wt: 321.8700

ACTION – Agent with affinity for the $\alpha 7$ nicotinic acetylcholine receptor, giving an IC₅₀ of 130 nM against [¹²⁵I]-bungarotoxin binding in rat hippocampal preparations ($\alpha 7$ receptors), compared to an IC₅₀ value of > 1000 nM against [³H]-cytisine binding in rat cortical membranes ($\alpha 4\beta 2$ receptors). It behaved as a partial agonist in electrophysiological tests using PC-12 cells. Potentially useful for the treatment of Alzheimer's disease, attention deficit hyperactivity disorder, anxiety, depression, schizophrenia, epilepsy, pain, Tourette's syndrome, Parkinson's disease, Huntington's chorea, neurodegenerative diseases and in smoking cessation. Other exemplified 1-azabicycloalkane derivatives are:



Compound	A	B	D	X	* Isomer	Formula
317252	S	CH	-CH2O-			C ₁₆ H ₁₉ NOS
317253	S	CH	-CH2O-		S	C ₁₆ H ₁₉ NOS
317255	S	CH	-(CH2)2-			C ₁₇ H ₂₁ NS
317256	S	CH	-(CH2)2-		(+)	C ₁₇ H ₂₁ NS
317257	S	CH	-(CH2)2-	HCl	(-)	C ₁₇ H ₂₃ NS.HCl
317258	S	CH	-COCH2-			C ₁₇ H ₁₉ NOS
318259	S	CH	-COCH2-	HCl	(-)	C ₁₇ H ₁₉ NOS.HCl
317260	S	N	-COCH2-			C ₁₆ H ₁₈ N ₂ OS
317261	O	CH	-COCH2-			C ₁₇ H ₁₉ NO ₂
317262	S	CH	-CH2-			C ₁₆ H ₁₉ NS



317254: C₁₈ H₂₁ N O

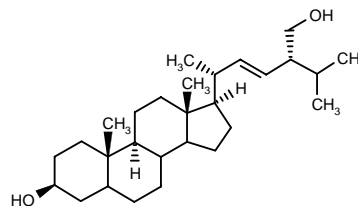
SOURCE – Mitsubishi Pharma.

REFERENCES

1. Fujio, M. et al. (Mitsubishi Pharma Corp.) *1-Azabicycloalkane cpds. and their medicinal use*. JP 2002030084.

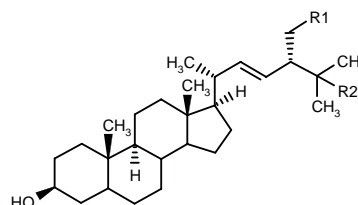
317276

22(*E*)-Ergostene-3 β ,28-diol



C₂₈ H₄₈ O₂; Mol wt: 416.6852

ACTION – Steroid derivative with neurotrophic activity for use in the treatment of Alzheimer's disease, senile dementia, Parkinson's disease and dyskinesia, among other neurodegenerative diseases. *In vitro*, compound was shown to promote neurite outgrowth in rat hypothalamus preparations at 1 μ g/ml. Other exemplified compounds are:



Compound	R1	R2	Formula
317277	H	H	C ₂₈ H ₄₈ O
317278	Me	OH	C ₂₉ H ₅₀ O ₂

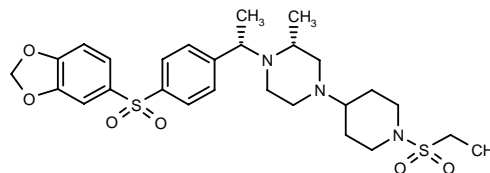
SOURCE – Kyorin.

REFERENCES

1. Kawahara, T. and Tachibana, Y. (Kyorin Pharmaceutical Co., Ltd.) *Agents for the regeneration of neuronal axon and their preparation method*. JP 2002030096.

317311

1-[1(*S*)-[4-(1,3-Benzodioxol-5-ylsulfonyl)phenyl]ethyl]-4-[1-(ethylsulfonyl)piperidin-4-yl]-2(*R*)-methylpiperazine



C₂₇ H₃₇ N₃ O₆ S₂; Mol wt: 563.7363

ACTION – Muscarinic M₂-selective ligand (K_i = 0.7 nM) with > 100-fold selectivity over M₁ receptors, able to produce a significant increase in acetylcholine levels in rat striatum after an oral dose of 10 mg/kg. Potentially useful for the treatment of Alzheimer's disease.

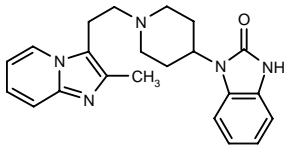
SOURCE – Schering-Plough.

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1. Kozlowski, J.A. et al. *Substituted 2-(R)-methyl piperazines as muscarinic M2 selective ligands*. Bioorg Med Chem Lett 2002, 12(5): 791.

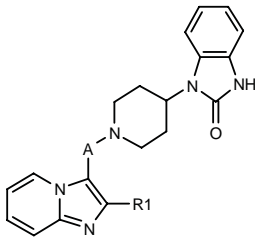
317464

1-[1-[2-(2-Methylimidazo[1,2-a]pyridin-3-yl)ethyl]piperidin-4-yl]-2,3-dihydro-1*H*-benzimidazol-2-one

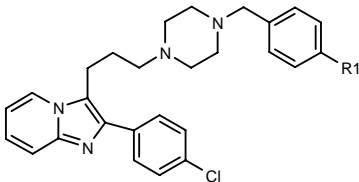


C22 H25 N5 O; Mol wt: 375.4735

ACTION – An inhibitor of the production of β -amyloid (A β) (IC₅₀ = 5 μ M), potentially useful for the treatment of Alzheimer's disease. Other exemplified imidazo[1,2-a]-pyridine derivatives include the following:



Compound	R1	A	Formula
317465	H	-(CH2)3-	C ₂₂ H ₂₅ N ₅ O
317467	Ph	-(CH2)3-	C ₂₈ H ₂₉ N ₅ O
317468	4-Cl-Ph	-(CH2)3-	C ₂₈ H ₂₈ ClN ₅ O
317471	Ph	(E)-CH=CHCO-	C ₂₈ H ₂₅ N ₅ O ₂



Compound	R1	Formula
317469	H	C ₂₇ H ₂₉ ClN ₄
317470	Cl	C ₂₇ H ₂₆ Cl ₂ N ₄

SOURCE – Boehringer Ingelheim.

REFERENCES

1. Fuchs, K. et al. (Boehringer Ingelheim Pharma KG) *Novel β -amyloid inhibitors, method for producing the same and the use thereof as medicaments*. DE 10040016, WO 0214313.

317531

L-Asparaginyl-glycyl-L-glutamyl-L-tryptophyl-L-aspartyl-L-leucyl-L-valyl-glycyl-L-isoleucyl-L-prolyl-glycyl-L-lysyl-L-arginyl-L-seryl-L-glutamyl-L-arginyl-L-phenylalanyl-L-tyrosyl-L-glutamyl-L-cysteinyl-L-cysteinyl-L-lysyl-L-glutamyl-L-prolyl-L-tyrosyl-L-prolyl-L-aspartyl-L-valyl-L-threonyl-L-phenylalanyl-L-threonyl-L-valine

C168 H248 N42 O51 S2; Mol wt: 3736.1820

ACTION – Peptide derived from the human $\alpha 7$ nicotinic acetylcholine receptor with affinity for β -amyloid peptide (A β), having the ability to inhibit the interaction of A β with the aforementioned receptor. Potentially useful for the diagnosis and treatment of Alzheimer's diseases and related neurodegenerative disorders. Another exemplified peptide is:

L-Seryl-glycyl-L-tyrosyl-L-isoleucyl-L-prolyl-L-asparaginyl-glycyl-L-glutamyl-L-tryptophyl-L-aspartyl-L-leucyl-L-valyl-glycyl-L-isoleucyl-L-prolyl-glycyl-L-lysyl-L-arginyl-L-seryl-L-glutamyl-L-arginyl-L-phenylalanyl-L-tyrosyl-L-glutamyl-L-cysteinyl-L-cysteinyl-L-lysyl-L-glutamyl-L-prolyl-L-tyrosyl-L-prolyl-L-aspartic acid

317532: C166 H242 N42 O51 S2

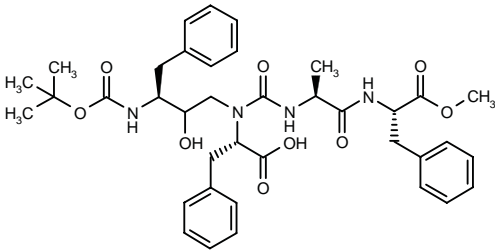
SOURCE – Ortho-McNeil.

REFERENCES

1. Lee, D.H.S. et al. (Ortho-McNeil Pharmaceutical, Inc.) *$\alpha 7$ Nicotinic receptor peptides as ligands for β amyloid peptides*. WO 0214351.

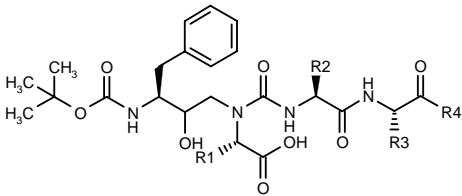
317551

N-[*N*-[3(*S*)-(tert-Butoxycarbonylamino)-2-hydroxy-4-phenylbutyl]-*N*-[1(*S*)-carboxy-2-phenylethyl]carbamoyl]-L-alanyl-L-phenylalanine methyl ester



C38 H48 N4 O9; Mol wt: 704.8162

ACTION – Secretase inhibitor able to inhibit the formation of β -amyloid peptide (A β), as demonstrated *in vitro* (IC₅₀ = 0.2 μ M). Potentially useful for the treatment of Alzheimer's disease and related disorders. Other exemplified compounds are:



Compound	R1	R2	R3	R4	Formula
317552	Me	i-Bu	CH2Ph	OMe	C ₃₈ H ₅₀ N ₄ O ₉
317554	CH2Ph	CH2Ph	CH2Ph	OMe	C ₄₄ H ₅₂ N ₄ O ₉
317555	CH2Ph	i-Bu	Me	OMe	C ₃₈ H ₅₀ N ₄ O ₉
317556	CH2Ph	i-Bu	CH2Ph	OMe	C ₄₁ H ₅₄ N ₄ O ₉
317558	CH2Ph	i-Bu	i-Bu	OMe	C ₃₈ H ₅₆ N ₄ O ₉
317559	CH2Ph	i-Bu	i-Pr	OMe	C ₃₇ H ₅₄ N ₄ O ₉
317562	CH2Ph	i-Pr	CH2Ph	OMe	C ₄₀ H ₅₂ N ₄ O ₉
317564	i-Bu	i-Bu	CH2Ph	OMe	C ₃₈ H ₅₆ N ₄ O ₉
317566	i-Pr	i-Bu	CH2Ph	OMe	C ₃₇ H ₅₄ N ₄ O ₉
317568	CH2Ph	i-Bu	i-Pr	-L-Ala-OMe	C ₄₀ H ₅₉ N ₅ O ₁₀
317569	CH2Ph	i-Bu	i-Pr	-L-Phe-OMe	C ₄₆ H ₆₃ N ₅ O ₁₀
317570	CH2Ph	i-Bu	i-Pr	-L-Leu-OMe	C ₄₃ H ₆₆ N ₅ O ₁₀
317571	CH2Ph	i-Bu	i-Pr	-L-Val-OMe	C ₄₂ H ₆₃ N ₅ O ₁₀

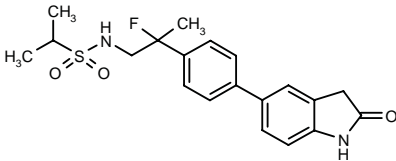
SOURCE – Brigham & Women’s Hospital, Boston, MA (US).

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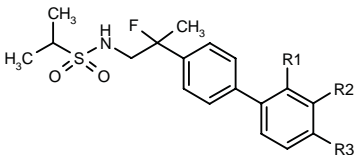
317584

N-[2-Fluoro-2-[4-(2-oxo-2,3-dihydro-1*H*-indol-5-yl)phenyl]-propyl]propane-2-sulfonamide isomer A



C20 H23 F N2 O3 S; Mol wt: 390.4767

ACTION – Glutamate receptor potentiator, potentially useful for the treatment of cognitive disorders including Alzheimer’s disease and attention deficit hyperactivity disorder, depression, psychosis and cognitive deficits related therewith. Other specifically claimed heterocyclic sulfonamides are:



Compound	R1	R2	R3	Isomer	Formula
318588	H	-CH2CONH-		B	C ₂₀ H ₂₃ FN ₂ O ₃ S
317589	H	-NHCOCH2-			C ₂₀ H ₂₃ FN ₂ O ₃ S
317590		-NHCOCH2-	H		C ₂₀ H ₂₃ FN ₂ O ₃ S
317592	H	-NHCONH-			C ₁₉ H ₂₂ FN ₃ O ₃ S

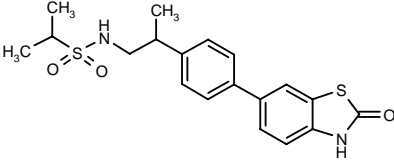
SOURCE – Lilly.

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1. Forman, S.L. et al. (Eli Lilly and Company) *Heterocyclic sulfonamide derivs*. WO 0214275.

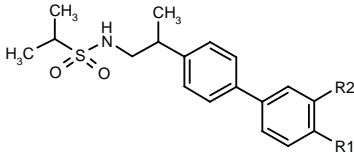
317594

N-[2-[4-(2-Oxo-2,3-dihydrobenzothiazol-6-yl)phenyl]-propyl]propane-2-sulfonamide



C19 H22 N2 O3 S2; Mol wt: 390.5258

ACTION – Glutamate receptor potentiator, potentially useful for the treatment of cognitive disorders including Alzheimer’s disease and attention deficit hyperactivity disorder, depression, psychosis and cognitive deficits related therewith. Other specifically claimed heterocycle-containing sulfonamide derivatives are:



Compound	R1,R2	Isomer	Formula
317595	-NHCOO-		C ₁₉ H ₂₂ N ₂ O ₄ S
317596	-NHCOCH2-		C ₂₀ H ₂₄ N ₂ O ₃ S
317597	-NHCOCH2-	R	C ₂₀ H ₂₄ N ₂ O ₃ S
317598	-NHCOCH2-	S	C ₂₀ H ₂₄ N ₂ O ₃ S
317599	-CH2CONH-		C ₂₀ H ₂₄ N ₂ O ₃ S
317600	-CH2CONH-	R	C ₂₀ H ₂₄ N ₂ O ₃ S
317601	-NHCOCH2CH2-		C ₂₁ H ₂₆ N ₂ O ₃ S
317602	-NHCONH-		C ₁₉ H ₂₃ N ₃ O ₃ S

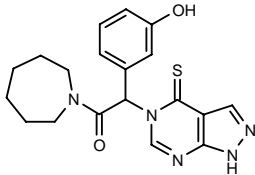
SOURCE – Lilly.

REFERENCES

1. Bender, D.M. et al. (Eli Lilly and Company) *Heterocyclic sulfonamide derivs*. WO 0214294.

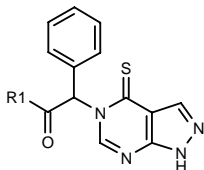
317938

5-[1-(3-Hydroxyphenyl)-2-oxo-2-(perhydroazepin-1-yl)ethyl]-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidine-4-thione



C19 H21 N5 O2 S; Mol wt: 383.4739

ACTION – Inhibitor of endoplasmic reticulum-associated amyloid- β peptide-binding protein (ERAB; IC_{50} = 0.051 μ M) that interferes with β -amyloid ($A\beta$) cytotoxicity. Potentially useful for the treatment of Alzheimer's disease, as well as other dementias and $A\beta$ -mediated cancer. Other exemplified pyrazole derivatives include the following:



Compound	R1	Formula
317944	perhydro-1-azepinyl	C ₁₉ H ₂₁ N ₅ OS
317946	perhydro-1-azocinyl	C ₂₀ H ₂₃ N ₅ OS
317947	4-OH-4-(4-Br-Ph)-1-Pip	C ₂₄ H ₂₂ BrN ₅ O ₂ S
317948	4-OH-4-Ph-1-Pip	C ₂₄ H ₂₃ N ₅ O ₂ S
317949	4-Bu-4-OH-1-Pip	C ₂₂ H ₂₇ N ₅ O ₂ S
317950	N(Et) ₂	C ₁₇ H ₁₉ N ₅ OS

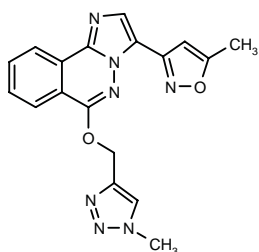
SOURCE – Agouron (Pfizer).

REFERENCES

1. Abreo, M.A. et al. (Agouron Pharmaceuticals, Inc.) *Pyrazole cpds., pharmaceutical compsns., and methods for modulating or inhibiting ERAB or HADH2 activity*. WO 0216365.

317951

3-(5-Methylisoxazol-3-yl)-6-(1-methyl-1*H*-1,2,3-triazol-4-ylmethoxy)imidazo[2,1-*a*]phthalazine



C₁₈H₁₅N₇O₂; Mol wt: 361.3635

ACTION – A representative compound from a series of imidazo[2,1-*a*]phthalazine derivatives with affinity for the α 5 subunit of GABA_A receptors. Compound acts as partial or full inverse agonist at this subunit but as an antagonist at α 1, α 2 and α 3 subunits. Potentially useful for the treatment of cognition disorders.

SOURCE – Merck Sharp & Dohme.

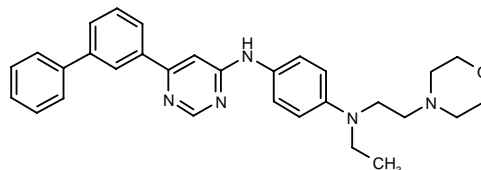
REFERENCES

1. Carling, W.R. et al. (Merck Sharp & Dohme Ltd.) *Imidazophthalazine derivs. as ligands for GABA_A receptors*. WO 0216363.

TREATMENT OF CEREBROVASCULAR DISEASES

317275

*N*¹-[6-(Biphenyl-3-yl)pyrimidin-4-yl]-*N*⁴-ethyl-*N*⁴-[2-(4-morpholinyl)ethyl]benzene-1,4-diamine



C₃₀H₃₃N₅O; Mol wt: 479.6247

ACTION – A representative compound from a series of *N*-phenylpyrimidine-4-amine derivatives with the ability to prevent neuronal cell death following traumatic events. It displayed neuroprotective effect in a rat model of transient cerebral ischemia at doses of 0.3 and 1.5 mg/kg i.v.

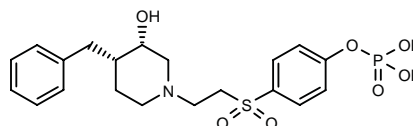
SOURCE – Ortho-McNeil.

REFERENCES

1. Grant, E.R. et al. (Ortho-McNeil Pharmaceutical, Inc.) *4-Pyrimidinamine derivs., pharmaceutical compsns. and related methods*. WO 0212198.

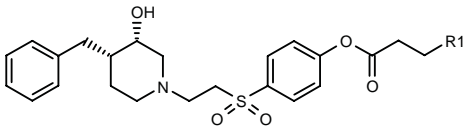
318014

Phosphoric acid 4-[2-[4(*S*)-benzyl-3(*S*)-hydroxypiperidin-1-yl]ethylsulfonyl]phenyl monoester



C₂₀H₂₆N O₇ P S; Mol wt: 455.4654

ACTION – A prodrug of a selective NMDA receptor antagonist reported to have better solubility and stability in solution when compared to the parent compound, and also a fast hydrolysis rate in plasma. The compound showed solubilities of > 37,600 and 594 μ g/ml, respectively, at pH 7 and 4. Rates of conversion to the parent compound of 41 and 35%, respectively, were obtained after 2 h in rat and human plasma. Potentially useful for the treatment of acute and chronic neurodegenerative disorders including stroke, brain trauma, Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis and neurodegeneration associated with bacterial or viral infections, as well as in the treatment of other CNS disorders such as schizophrenia, anxiety, depression and acute and chronic pain. Other specifically claimed compounds are:



Compound	R1	Formula
318015	CO2H	C ₂₄ H ₂₉ NO ₇ S
318017	NHCOCH2CH2NH2	C ₂₆ H ₃₅ N ₃ O ₆ S

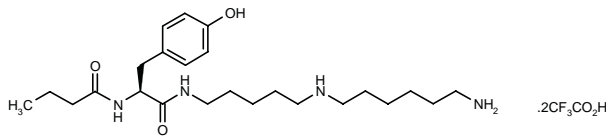
SOURCE – Roche.

REFERENCES

1. Alanine, A. et al. (F. Hoffmann-La Roche AG) *Produgs to NMDA receptor ligands*. WO 0216321.

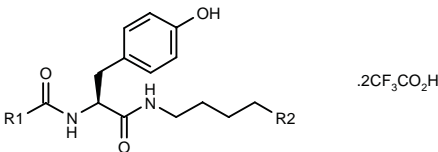
318179

N¹-[5-(6-Aminohexylamino)pentyl]-N²-butyryl-L-tyrosinamide bis(trifluoroacetate)



C24 H42 N4 O3 . 2 C2 H F3 O2; Mol wt: 662.6646

ACTION – Potent and selective AMPA receptor antagonist that demonstrated *in vitro* activity against AMPA receptors in voltage-clamp assays using *Xenopus* oocytes. Potentially useful for the treatment of stroke, cerebral ischemia, head and spinal cord trauma, Parkinson’s disease, tardive dyskinesia, Alzheimer’s disease, Huntington’s chorea, AIDS encephalopathy, amyotrophic lateral sclerosis, epilepsy, spasms, hypoxia, hypoglycemic neuronal damage, ocular damage, migraine, psychosis, pain, anxiety, emesis, retinal neuropathy and tinnitus. Other exemplified substituted polyamine compounds are:



Compound	R1	R2	Formula
318180	Pr	NH(CH2)7NH2	C ₂₄ H ₄₂ N ₄ O ₃ ·2C ₂ HF ₃ O ₂
318181	3-Pyr	(CH2)4NH(CH2)3NH2	C ₂₆ H ₃₉ N ₅ O ₃ ·2C ₂ HF ₃ O ₂
318182	4-Pyr	(CH2)4NH(CH2)3NH2	C ₂₆ H ₃₉ N ₅ O ₃ ·2C ₂ HF ₃ O ₂
318183	cyclohexyl	(CH2)4NH(CH2)3NH2	C ₂₇ H ₄₆ N ₄ O ₃ ·2C ₂ HF ₃ O ₂
318185	C5H11	(CH2)4NH(CH2)3NH2	C ₂₆ H ₄₆ N ₄ O ₃ ·2C ₂ HF ₃ O ₂
318186	t-BuCH2	(CH2)4NH(CH2)3NH2	C ₂₆ H ₄₆ N ₄ O ₃ ·2C ₂ HF ₃ O ₂

SOURCE – Lundbeck.

REFERENCES

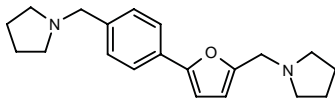
1. Stroemgaard, K. et al. (H. Lundbeck A/S) *Substd. polyamine cpds*. WO 0216314.

RESPIRATORY DRUGS

TREATMENT OF UPPER RESPIRATORY TRACT DISORDERS

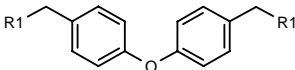
317338

1-[4-[5-(Pyrrolidin-1-ylmethyl)furan-2-yl]benzyl]pyrrolidine

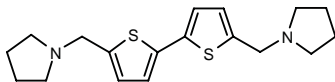


C20 H26 N2 O; Mol wt: 310.4384

ACTION – Histamine H₃ receptor antagonist (K_i = 0.4 nM), potentially useful for the treatment of nasal congestion, allergic rhinitis and upper airways allergic responses, as well as sleep disorders, arousal/vigilance disorders, migraine, asthma, dementia, mild cognitive impairment, Alzheimer’s disease, epilepsy, narcolepsy, eating disorders, motion sickness, vertigo, attention deficit hyperactivity disorder, learning disorders, memory retention disorders and schizophrenia. Other exemplified bicyclic compounds are:



Compound	R1	Formula
317339	1-pyrrolidinyl	C ₂₂ H ₂₈ N ₂ O
317340	1-Pip	C ₂₄ H ₃₂ N ₂ O



317341: C18 H24 N2 S2

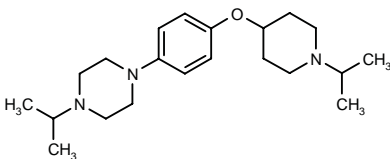
SOURCE – Ortho-McNeil.

REFERENCES

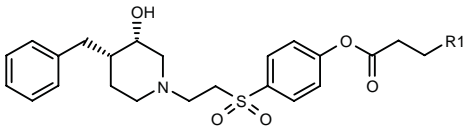
1. Bogenstaetter, M. et al. (Ortho-McNeil Pharmaceutical, Inc.) *Bicyclic cpds*. WO 0212224.

317342

1-Isopropyl-4-[4-(1-isopropylpiperidin-4-yloxy)phenyl]-piperazine



C21 H35 N3 O; Mol wt: 345.5275



Compound	R1	Formula
318015	CO2H	C ₂₄ H ₂₉ NO ₇ S
318017	NHCOCH2CH2NH2	C ₂₆ H ₃₅ N ₃ O ₆ S

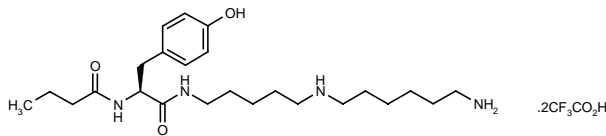
SOURCE – Roche.

REFERENCES

1. Alanine, A. et al. (F. Hoffmann-La Roche AG) *Produgs to NMDA receptor ligands*. WO 0216321.

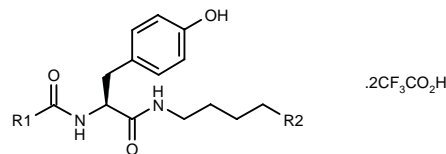
318179

N¹-[5-(6-Aminohexylamino)pentyl]-N²-butyryl-L-tyrosinamide bis(trifluoroacetate)



C24 H42 N4 O3 . 2 C2 H F3 O2; Mol wt: 662.6646

ACTION – Potent and selective AMPA receptor antagonist that demonstrated *in vitro* activity against AMPA receptors in voltage-clamp assays using *Xenopus* oocytes. Potentially useful for the treatment of stroke, cerebral ischemia, head and spinal cord trauma, Parkinson’s disease, tardive dyskinesia, Alzheimer’s disease, Huntington’s chorea, AIDS encephalopathy, amyotrophic lateral sclerosis, epilepsy, spasms, hypoxia, hypoglycemic neuronal damage, ocular damage, migraine, psychosis, pain, anxiety, emesis, retinal neuropathy and tinnitus. Other exemplified substituted polyamine compounds are:



Compound	R1	R2	Formula
318180	Pr	NH(CH2)7NH2	C ₂₄ H ₄₂ N ₄ O ₃ ·2C ₂ HF ₃ O ₂
318181	3-Pyr	(CH2)4NH(CH2)3NH2	C ₂₆ H ₃₉ N ₅ O ₃ ·2C ₂ HF ₃ O ₂
318182	4-Pyr	(CH2)4NH(CH2)3NH2	C ₂₆ H ₃₉ N ₅ O ₃ ·2C ₂ HF ₃ O ₂
318183	cyclohexyl	(CH2)4NH(CH2)3NH2	C ₂₇ H ₄₆ N ₄ O ₃ ·2C ₂ HF ₃ O ₂
318185	C5H11	(CH2)4NH(CH2)3NH2	C ₂₆ H ₄₆ N ₄ O ₃ ·2C ₂ HF ₃ O ₂
318186	t-BuCH2	(CH2)4NH(CH2)3NH2	C ₂₆ H ₄₆ N ₄ O ₃ ·2C ₂ HF ₃ O ₂

SOURCE – Lundbeck.

REFERENCES

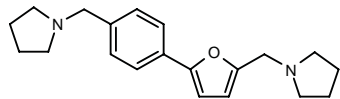
1. Stroemgaard, K. et al. (H. Lundbeck A/S) *Substd. polyamine cpds*. WO 0216314.

RESPIRATORY DRUGS

TREATMENT OF UPPER RESPIRATORY TRACT DISORDERS

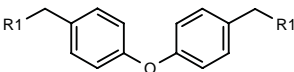
317338

1-[4-[5-(Pyrrolidin-1-ylmethyl)furan-2-yl]benzyl]pyrrolidine

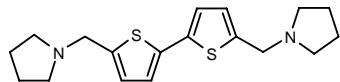


C20 H26 N2 O; Mol wt: 310.4384

ACTION – Histamine H₃ receptor antagonist (K_i = 0.4 nM), potentially useful for the treatment of nasal congestion, allergic rhinitis and upper airways allergic responses, as well as sleep disorders, arousal/vigilance disorders, migraine, asthma, dementia, mild cognitive impairment, Alzheimer’s disease, epilepsy, narcolepsy, eating disorders, motion sickness, vertigo, attention deficit hyperactivity disorder, learning disorders, memory retention disorders and schizophrenia. Other exemplified bicyclic compounds are:



Compound	R1	Formula
317339	1-pyrrolidinyl	C ₂₂ H ₂₈ N ₂ O
317340	1-Pip	C ₂₄ H ₃₂ N ₂ O



317341: C18 H24 N2 S2

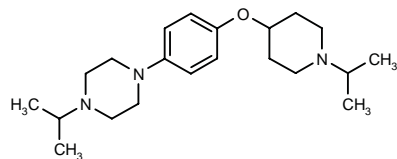
SOURCE – Ortho-McNeil.

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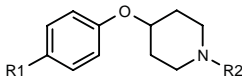
317342

1-Isopropyl-4-[4-(1-isopropylpiperidin-4-yloxy)phenyl]-piperazine



C21 H35 N3 O; Mol wt: 345.5275

ACTION – Histamine H₃ receptor antagonist (K_i = 0.2 nM), potentially useful for the treatment of nasal congestion, allergic rhinitis and upper airways allergic responses, as well as sleep disorders, arousal/vigilance disorders, migraine, asthma, dementia, mild cognitive impairment, Alzheimer’s disease, epilepsy, narcolepsy, eating disorders, motion sickness, vertigo, attention deficit hyperactivity disorder, learning disorders, memory retention disorders and schizophrenia. Other exemplified aryloxy piperidines are:



Compound	R1	R2	Formula
317343	1-Pip-CH2	CH(Me)Et	C ₂₁ H ₃₄ N ₂ O
317344	1-Pip-CH2	cyclopentyl	C ₂₂ H ₃₄ N ₂ O
317345	1-Pip-CH2	i-Pr	C ₂₀ H ₃₂ N ₂ O
317346	1-Piz	i-Pr	C ₁₈ H ₂₉ N ₃ O

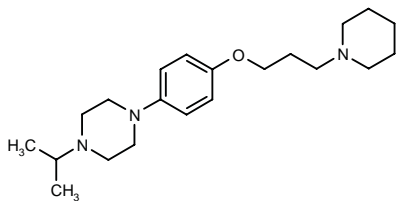
SOURCE – Ortho-McNeil.

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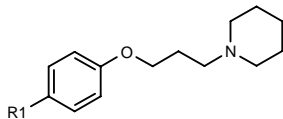
317347

1-Isopropyl-4-[4-[3-(1-piperidinyl)propoxy]phenyl]-piperazine

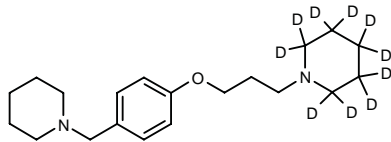


C₂₁ H₃₅ N₃ O; Mol wt: 345.5275

ACTION – Histamine H₃ receptor antagonist (K_i = 0.26 nM), potentially useful for the treatment of nasal congestion, allergic rhinitis and upper airways allergic responses, as well as sleep disorders, arousal/vigilance disorders, migraine, asthma, dementia, mild cognitive impairment, Alzheimer’s disease, epilepsy, narcolepsy, eating disorders, motion sickness, vertigo, attention deficit hyperactivity disorder, learning disorders, memory retention disorders and schizophrenia. Other exemplified aryloxyalkylamines are:



Compound	R1	Formula
317348	1-Pip-CH2	C ₂₀ H ₃₂ N ₂ O
317349	1-Pip-CH2CH2O	C ₂₁ H ₃₄ N ₂ O ₂
317350	1-Pip-(CH2)3O	C ₂₂ H ₃₆ N ₂ O ₂
317351	5-[1-Pip-(CH2)3S]-1-tetrazolyl	C ₂₃ H ₃₆ N ₆ OS
317352	1-Pip-CH2	C ₂₀ H ₃₂ N ₂ O
317353	1,2,3,4-tetrahydro-2-isoquinoliny-CH2	C ₂₄ H ₃₂ N ₂ O
317354	1-Me-2-pyrrolidiny	C ₁₉ H ₃₀ N ₂ O
317355	4-(2-Pyr-NH)-1-Pip-CH2	C ₂₅ H ₃₆ N ₄ O
317356	4-[PhCH2N(Me)]-1-Pip-CH2	C ₂₈ H ₄₁ N ₃ O
317358	4-OH-1-Pip-CH2	C ₂₀ H ₃₂ N ₂ O ₂
317359	4-morpholinyl-CH2	C ₁₉ H ₃₀ N ₂ O ₂



317357: C₂₀ H₂₂ D₁₀ N₂ O

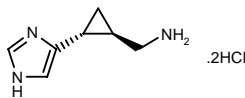
SOURCE – Ortho-McNeil.

REFERENCES

1. Apodaca, R. et al. (Ortho-McNeil Pharmaceutical, Inc.) *Non-imidazole aryloxyalkylamines*. WO 0212190, WO 0212214.

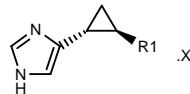
317433

trans-1-[2-(1*H*-Imidazol-4-yl)cyclopropyl]methanamine dihydrochloride



C₇ H₁₁ N₃ . 2HCl; Mol wt: 210.1067

ACTION – Histamine H₃ receptor antagonist that inhibited the binding of [³H]-*N*^α-methylhistamine to H₃ receptors from rat cortical membranes with a K_i of 4.5 nM. Potentially useful for the treatment of allergy, cardiovascular diseases, inflammation, hypotension, glaucoma, sleep disorders, hyper- and hypomotility disorders of the gastrointestinal tract, CNS hypo- and hyperactivity, Alzheimer’s disease, schizophrenia, obesity and migraine. Other exemplified imidazoles are:



Compound	R1	X	Formula
317434	CN	CF ₃ CO ₂ H	C ₇ H ₇ N ₃ .C ₂ H ₃ HF ₃ O ₂
317435	CONH ₂	CF ₃ CO ₂ H	C ₇ H ₉ N ₃ O.C ₂ H ₃ HF ₃ O ₂
317436	C(=NH)NH ₂	2CF ₃ CO ₂ H	C ₇ H ₁₀ N ₄ .2C ₂ H ₃ HF ₃ O ₂
317437	CH=NOH		C ₇ H ₉ N ₃ O
317438	CH ₂ OH	CF ₃ CO ₂ H	C ₇ H ₁₀ N ₂ O.C ₂ H ₃ HF ₃ O ₂
317439	C(=NH)NHMe	2HCl	C ₈ H ₁₂ N ₄ .2HCl

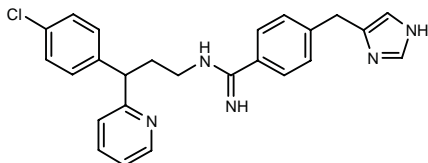
SOURCE – Gliatech.

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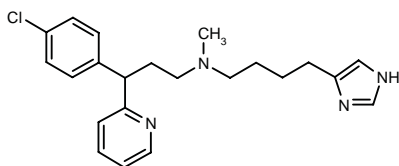
318136

N-[3-(4-Chlorophenyl)-3-(2-pyridyl)propyl]-4-(1*H*-imidazol-4-ylmethyl)benzamidine



C25 H24 Cl N5; Mol wt: 429.9526

ACTION – Dual histamine H₁/H₃ receptor antagonist (K_i = 136 and 58 nM for H₁ and H₃ receptors, respectively) proven active in a guinea pig H₃-antagonist model. Potentially useful for the treatment of allergic rhinitis. Another related compound is:



318139: C22 H27 Cl N4

SOURCE – Schering-Plough.

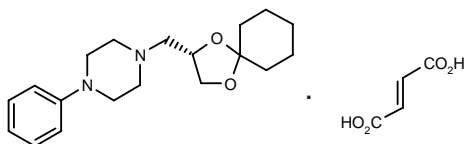
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1. Aslanian, R. et al. *Design and synthesis of novel dual histamine H₁/H₃ receptor antagonists based on the H₁ receptor antagonist chlorpheniramine*. 223rd ACS Natl Meet (April 7-11, Orlando) 2002, Abst MEDI 63.

DF-1689A

317206

(–)-1-[1,4-Dioxaspiro[4.5]dec-2(*S*)-ylmethyl]-4-phenyl-piperazine fumarate



C19 H28 N2 O2 . C4 H4 O4; Mol wt: 432.5138

ACTION – A representative compound from a series of 4-(piperazin-1-ylmethyl)dioxolane derivatives with potential as an antitussive agent. DF-1689A was able to inhibit capsaicin-induced cough by 47.3% following i.v. administration to pigs at a dose of 10 mg/kg. The inhibition rates were 34.6 and 27.3%, respectively, when calculated 15 and 30 min after drug administration, thus proving its long-lasting effect. Compound also demonstrated antitussive activity when administered by aerosol.

SOURCE – Dompé.

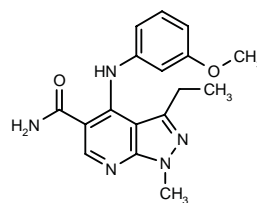
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ASTHMA THERAPY

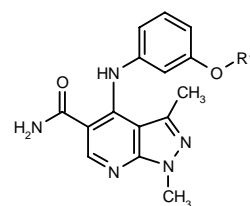
316987

3-Ethyl-4-(3-methoxyphenylamino)-1-methyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide



C17 H19 N5 O2; Mol wt: 325.3701

ACTION – Phosphodiesterase type 4 (PDE4) inhibitor (IC₅₀ = 0.003 μM), potentially useful for the treatment of inflammatory diseases such as asthma, obstructive pulmonary disease, sepsis, nephritis and hepatitis, diabetes, allergic diseases including allergic rhinitis, conjunctivitis and atopic dermatitis, autoimmune disorders (ulcerative colitis, Crohn's disease, rheumatism, psoriasis, multiple sclerosis, etc.), osteoporosis, obesity, depression, Parkinson's disease, ischemia–reperfusion disorders and leukemia, among others. Other exemplified pyrazolo[3,4-*b*]pyridine-5-carboxamide compounds include the following:



Compound	R1	Formula
316989	Me	C ₁₆ H ₁₇ N ₅ O ₂
316991	1-CO2Me-3(S)-pyrrolidinyl	C ₂₁ H ₂₄ N ₆ O ₄

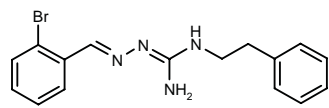
SOURCE – Ono.

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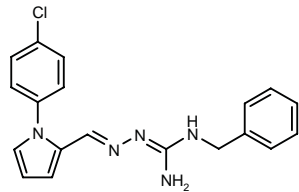
317046

*N*²-(2-Bromobenzylideneamino)-*N*¹-(2-phenylethyl)-guanidine

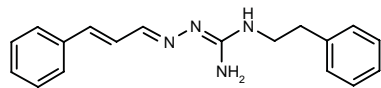


C16 H17 Br N4; Mol wt: 345.2423

ACTION – Melanocortin receptor ligand with *K*_i values of 1.24, 7.96, 1.34 and 5.80 μM, respectively, against MC₁, MC₃, MC₄ and MC₅ receptors. Potentially useful for the treatment of a broad range of inflammatory, mental, endocrine, sexual and cardiovascular disorders including pain, type 2 diabetes, obesity, anorexia, melanoma and ischemia, as well as for stimulating central and peripheral nerve regeneration. In particular, it may be useful for inflammatory conditions caused by or associated with allergy, hypersensitivity, bacterial or viral infection, fever, autoimmune diseases and radiation damage. Other exemplified 2-aminoguanidine derivatives are:



317048: C19 H18 Cl N5



317049: C18 H20 N4

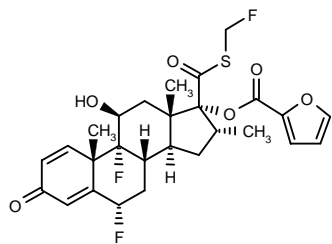
SOURCE – Melacure Therapeutics.

REFERENCES

1. Pett, C.P. et al. (Melacure Therapeutics) *Cpds. acting as melanocortin receptor ligands*. WO 0212178.

317132

6α,9α-Difluoro-17α-(furan-2-ylcarbonyloxy)-11β-hydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17-carbothioic acid *S*-(fluoromethyl) ester



C27 H29 F3 O6 S; Mol wt: 538.5801

ACTION – A representative compound from a series of androstane-17β-carbothioic acid derivatives with anti-inflammatory and antiallergic properties. This compound demonstrated glucocorticoid-agonist activity *in vitro*. *In vivo*, it was able to inhibit lung eosinophilia by 69% following intratracheal administration to ovalbumin-

sensitized rats as a single dose of 30 μg, and it produced a 67% reduction in thymus weight after 3 daily doses of 100 μg, having a better therapeutic index than fluticasone propionate in this animal model. In human hepatocytes, this compound was metabolized 5-fold more rapidly than the reference compound. In pharmacokinetic studies in pigs, the systemic exposure of both compounds was similar following i.v. administration (0.1 mg/kg), while it was markedly reduced for the compound of the invention following intratracheal administration at the same dose.

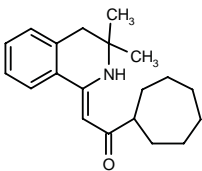
SOURCE – GlaxoSmithKline.

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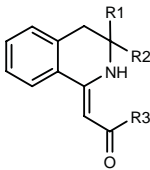
317269

(*Z*)-1-Cycloheptyl-2-(3,3-dimethyl-1,2,3,4-tetrahydroisoquinolin-1-ylidene)ethanone



C20 H27 N O; Mol wt: 297.4393

ACTION – Cannabinoid CB₂ receptor agonist, as demonstrated by its ability to inhibit forskolin-stimulated cAMP production in CB₂-transfected CHO cells (IC₅₀ = 0.4 nM). Potentially useful for the treatment of inflammatory and immune disorders including asthma, allergic rhinitis, atopic dermatitis, autoimmune diseases, rheumatism, immunodeficiency, postoperative pain and cancer-related pain. Other exemplified 3,4-dihydroisoquinoline derivatives are:



Compound	R1	R2	R3	Formula
317270	Me	Me	cyclohexyl	C ₁₉ H ₂₅ NO
317271	-CH2CH2OCH2CH2-		Ph	C ₂₁ H ₂₁ NO ₂

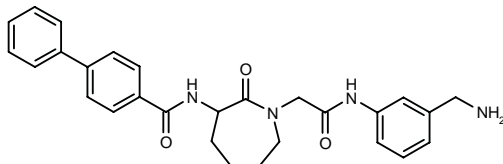
SOURCE – Ono.

REFERENCES

1. Ogawa, M. et al. (Ono Pharmaceutical Co., Ltd.) *3,4-Dihydroisoquinoline deriv. cpds. and drugs containing these cpds. as the active ingredient*. WO 0210135.

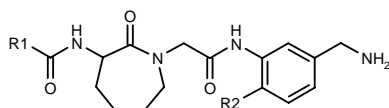
317292

N-[1-[*N*-[3-(Aminomethyl)phenyl]carbamoymethyl]-2-oxoperhydroazepin-3-yl]biphenyl-4-carboxamide



C28 H30 N4 O3; Mol wt: 470.5700

ACTION – An inhibitor of serine proteases, particularly trypsin, potentially useful for the treatment of asthma and related disorders. Other specifically claimed lactam compounds include the following:



Compound	R1	R2	Formula
317293	4-Ph-Ph	Me	C ₂₉ H ₃₂ N ₄ O ₃
317294	4-Ph-Ph	Cl	C ₂₈ H ₂₉ ClN ₄ O ₃
317295	CH ₂ CH(Ph) ₂	H	C ₃₀ H ₃₄ N ₄ O ₃

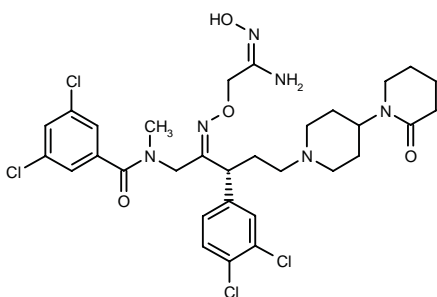
SOURCE – Bristol-Myers Squibb.

REFERENCES

1. Bisacchi, G.S. et al. (Bristol-Myers Squibb Co.) *Lactam cpds. and their use as inhibitors of serine proteases and method*. WO 0212196.

317329

N-[2(*E*)-[2-Amino-2(*E*)-(hydroxyimino)ethoxyimino]-3(*R*)-(3,4-dichlorophenyl)-5-(2-oxo-1,4'-bipiperidin-1'-yl)pentyl]-3,5-dichloro-*N*-methylbenzamide



C31 H38 Cl4 N6 O4; Mol wt: 700.4912

ACTION – Nonselective neurokinin antagonist with nanomolar binding affinity for both NK₁ and NK₂ receptors (K_i = 7.4 and 11.5 nM, respectively). In guinea pigs, compound showed oral antagonist activity at both NK₁ and NK₂ receptors: a dose of 10 mg/kg inhibited substance P-induced microvascular airways permeability (NK₁ receptor-mediated) and β-Ala-neurokinin A-induced bronchospasm (NK₂ receptor-mediated) by 91 and 94%, respectively. Compound exhibited a good pharmacokinetic profile after oral administration to rats. Potentially useful for the treatment of asthma.

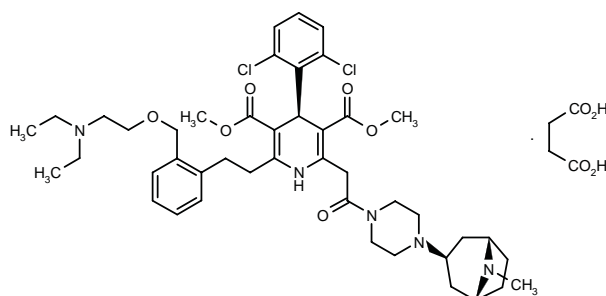
SOURCE – Schering-Plough.

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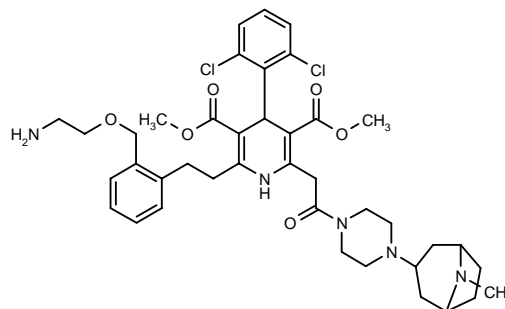
317361

(–)-4(*R*)-(2,6-Dichlorophenyl)-2-[2-[2-(diethyl-amino)ethoxymethyl]phenyl]ethyl]-6-[2-[4-(8-methyl-8-azabicyclo[3.2.1]oct-3-*exo*-yl)piperazin-1-yl]-2-oxoethyl]-1,4-dihydropyridine-3,5-dicarboxylic acid dimethyl diester succinate



C44 H59 Cl2 N5 O6 . C4 H6 O4; Mol wt: 942.9725

ACTION – Bradykinin antagonist, potentially useful for the treatment of inflammation, asthma, allergic rhinitis and pain. Further applications include arthritis, cystitis, cerebral edema, liver cirrhosis, Alzheimer's disease, allergies, pancreatitis, viral infections, head injury, hepatorenal failure, diabetes, cancer, glaucoma, amyotrophic lateral sclerosis, stroke, migraine, pruritus, chronic obstructive pulmonary disease and sepsis. Another specifically claimed 1,4-dihydropyridine-3,5-dicarboxylic acid derivative is:



317366: C40 H51 Cl2 N5 O6

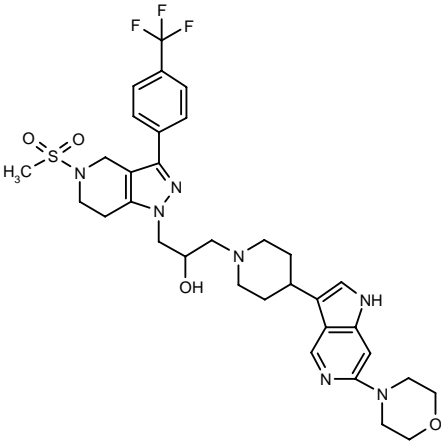
SOURCE – Pfizer.

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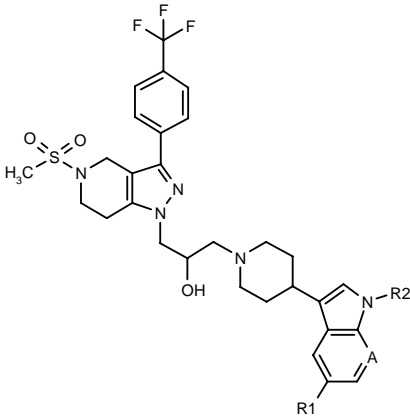
317545

1-[5-(Methylsulfonyl)-3-[4-(trifluoromethyl)phenyl]-4,5,6,7-tetrahydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl]-3-[4-[6-(4-morpholinyl)-1*H*-pyrrolo[3,2-*c*]pyridin-3-yl]piperidin-1-yl]propan-2-ol

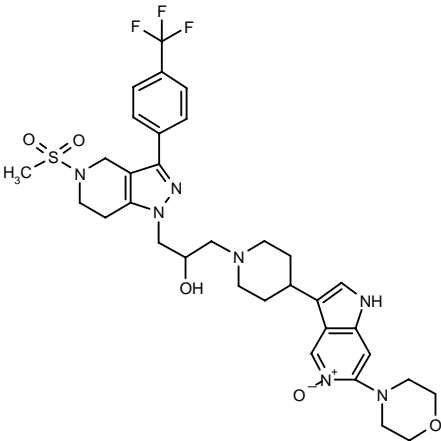


C33 H40 F3 N7 O4 S; Mol wt: 687.7840

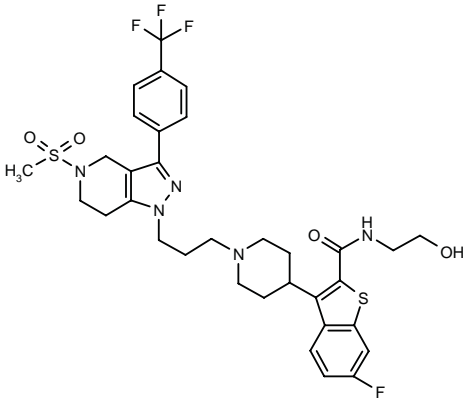
ACTION – Cathepsin S inhibitor (IC₅₀ = 0.02 μM), potentially useful for the treatment of autoimmune diseases, particularly asthma, transplant rejection, lupus and rheumatoid arthritis. Other exemplified pyrazole derivatives are:



Compound	R1	R2	A	Formula
317548	CN	H	CH	C ₃₁ H ₃₃ F ₃ N ₆ O ₃ S
317549	OMe	H	CH	C ₃₁ H ₃₆ F ₃ N ₅ O ₄ S
317550	H	4-morpholinyl-CH2CH2	N	C ₃₅ H ₄₄ F ₃ N ₇ O ₄ S



317546: C33 H40 F3 N7 O5 S



317547: C33 H37 F4 N5 O4 S2

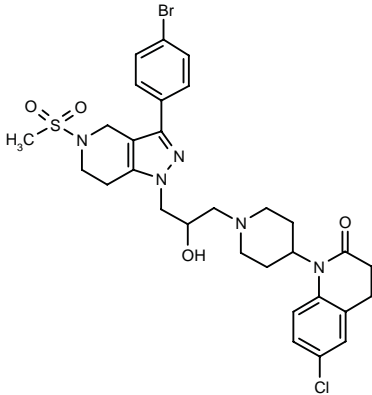
SOURCE – Ortho-McNeil.

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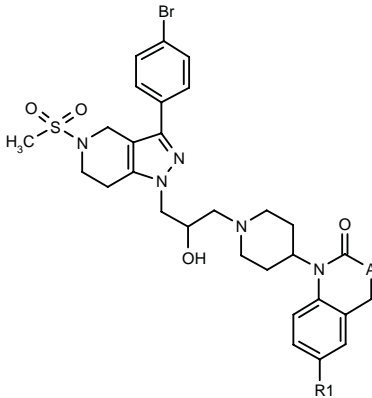
317553²

1-[1-[3-[3-(4-Bromophenyl)-5-(methylsulfonyl)-4,5,6,7-tetrahydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl]-2-hydroxypropyl]piperidin-4-yl]-6-chloro-1,2,3,4-tetrahydroquinolin-2-one

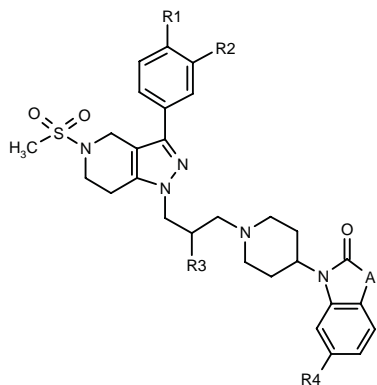


C30 H35 Br Cl N5 O4 S; Mol wt: 677.0605

ACTION – Cathepsin S inhibitor (IC₅₀ = 0.02 μM), potentially useful for the treatment of autoimmune diseases, particularly asthma, transplant rejection, lupus and rheumatoid arthritis. Other exemplified pyrazole derivatives are:



Compound	R1	A	Formula
317557 ²	Cl	NH	C ₂₉ H ₃₄ BrClN ₆ O ₄ S
317560 ²	H	CH2	C ₃₀ H ₃₆ BrN ₅ O ₄ S



Compound	R1	R2	R3	R4	Isomer	A	Formula
317561 ^{1,2}	CF3	H	H	H		CH2	C ₃₀ H ₃₄ F ₃ N ₅ O ₃ S
317563 ²	Cl	Me	OH	H		CH2	C ₃₀ H ₃₆ ClN ₅ O ₄ S
317565 ²	Cl	Me	OH	H		NH	C ₂₉ H ₃₅ ClN ₆ O ₄ S
317567 ²	CF3	H	OH	Cl	R	N(Me)	C ₃₀ H ₃₄ ClF ₃ N ₆ O ₄ S

SOURCE – Ortho-McNeil.

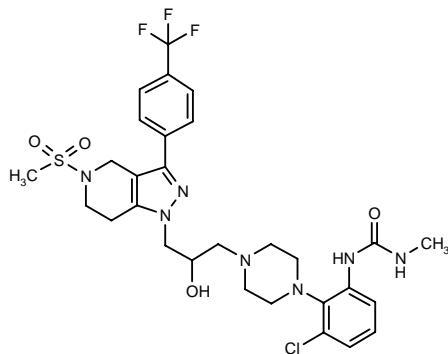
REFERENCES

1. Butler, C.R. et al. (Ortho-McNeil Pharmaceutical, Inc.) *A method for treating allergies using substd. pyrazoles*. WO 0220011.

2. Butler, C.R. et al. (Ortho-McNeil Pharmaceutical, Inc.) *Substd. pyrazoles*. WO 0214315.

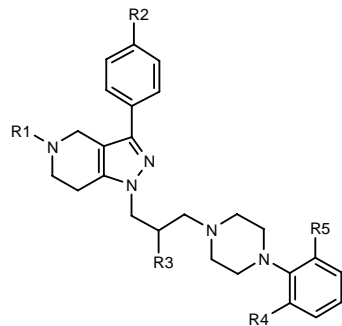
317572^{1,2}

N¹-[3-Chloro-2-[4-[2-hydroxy-3-[5-(methylsulfonyl)-3-[4-(trifluoromethyl)phenyl]-4,5,6,7-tetrahydro-1 H-pyrazolo-[4,3-c]pyridin-1-yl]propyl]piperazin-1-yl]phenyl]-N³-methyleurea

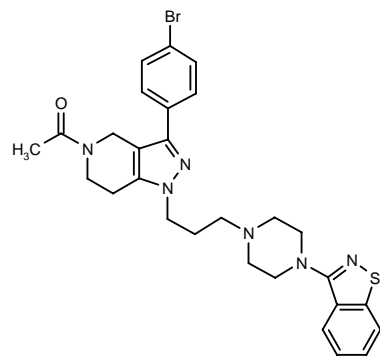


C29 H35 Cl F3 N7 O4 S; Mol wt: 670.1535

ACTION – Cathepsin S inhibitor (IC₅₀ = 0.04 μM), potentially useful for the treatment of autoimmune diseases, particularly asthma, transplant rejection, lupus and rheumatoid arthritis. Other exemplified pyrazole derivatives are:



Compound	R1	R2	R3	R4	R5	Formula
317573 ²	CONH2	I	OH	H	Me	C ₂₇ H ₃₃ N ₆ O ₂
317574 ²	SO2Me	CF3	H	H	Me	C ₂₈ H ₃₄ F ₃ N ₅ O ₂ S
317575 ²	SO2Me	Br	H	H	NO2	C ₂₈ H ₃₁ BrN ₆ O ₄ S
317577 ²	SO2Me	CF3	H	Cl	NHCONH2	C ₂₈ H ₃₃ ClF ₃ N ₇ O ₃ S
317578 ²	SO2Me	CF3	OH	CN	CN	C ₂₉ H ₃₀ F ₃ N ₇ O ₃ S
317582 ²	SO2Me	CF3	OH	Cl	CO2Me	C ₂₉ H ₃₃ ClF ₃ N ₅ O ₅ S
317583 ²	SO2Me	CF3	OH	NHSO2Me	CO2Me	C ₃₀ H ₃₇ F ₃ N ₆ O ₇ S ₂



317576²: C28 H31 Br N6 O S

SOURCE – Ortho-McNeil.

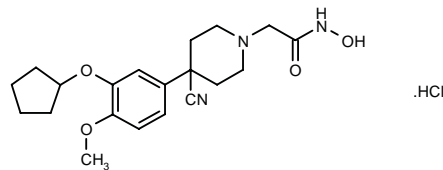
REFERENCES

1. Breitenbucher, J.G. et al. (Ortho-McNeil Pharmaceutical, Inc.) *Method for treating allergies using substd. pyrazoles*. WO 0220012.

2. Breitenbucher, J.G. et al. (Ortho-McNeil Pharmaceutical, Inc.) *Substd. pyrazoles*. WO 0214314.

317676

2-[4-Cyano-4-[3-(cyclopentyloxy)-4-methoxyphenyl]piperidin-1-yl]acetohydroxamic acid hydrochloride



C20 H27 N3 O4 . HCl; Mol wt: 409.9112

ACTION – Phosphodiesterase type 4 (PDE4) inhibitor (IC_{50} = 0.03 μ M), potentially useful for the treatment of inflammatory diseases such as asthma, obstructive pulmonary disease, sepsis, sarcoidosis, nephritis, hepatitis and enteritis, diabetes, allergic conditions including allergic rhinitis, allergic conjunctivitis and atopic dermatitis, autoimmune diseases such as ulcerative colitis, Crohn’s disease, rheumatism, psoriasis, multiple sclerosis, as well as other PDE4-mediated conditions.

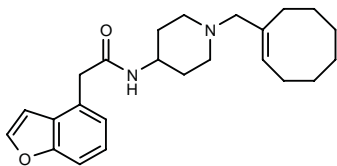
SOURCE – Ono.

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1. Nakai, H. and Kishikawa, K. (Ono Pharmaceutical Co., Ltd.) *Piperidine derivs. and drugs containing these derivs. as the active ingredient.* WO 0214280.

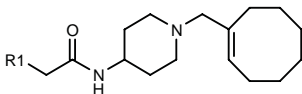
317952

2-(1-Benzofuran-4-yl)-N-[1-(1-cycloocten-1-ylmethyl)-piperidin-4-yl]acetamide

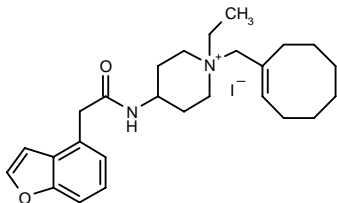


C24 H32 N2 O2; Mol wt: 380.5288

ACTION – Chemokine CCR3 receptor antagonist, potentially useful for the treatment of immune and inflammatory disorders including asthma, eczema, conjunctivitis, allergic rhinitis, atopic dermatitis, pruritus, psoriasis, chronic obstructive pulmonary disease, adult respiratory distress syndrome, arthritis, Crohn’s disease, ulcerative colitis, inflammatory bowel disease, septic shock, stroke, cardiac and renal reperfusion injury, glomerulonephritis, thrombosis, Alzheimer’s disease, transplant rejection, HIV infection and atherosclerosis. Other specifically claimed bicyclic heteroaryl derivatives are:



Compound	R1	Formula
317953	2-Cl-6-benzothiazolyl	C ₂₃ H ₃₀ ClN ₃ OS
317954	5-Cl-3-benzothieryl	C ₂₄ H ₃₁ ClN ₂ OS
317955	2-MeS-5-benzoxazolyl	C ₂₄ H ₃₃ N ₃ O ₂ S



317956: C26 H37 I N2 O2

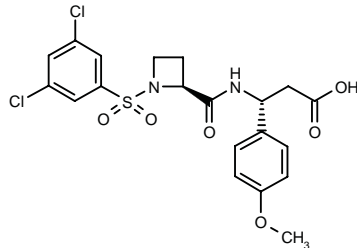
SOURCE – Celltech Group.

REFERENCES

1. Owen, D.A. et al. (Celltech Group plc) *Bicyclic heteroaromatic derivs. for the treatment of immune and inflammatory disorders.* WO 0216353.

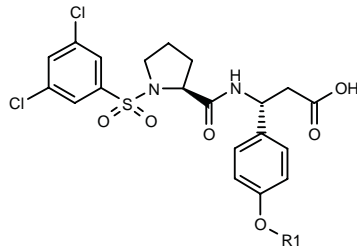
318573

3(R)-[1-(3,5-Dichlorophenylsulfonyl)azetidin-2(S)-ylcarboxamido]-3-(4-methoxyphenyl)propionic acid



C20 H20 Cl2 N2 O6 S; Mol wt: 487.3580

ACTION – Potent, specific and orally available VLA-4 ($\alpha_4\beta_1$ integrin) antagonist (IC_{50} = 0.49 nM) with > 500-fold selectivity over $\alpha_4\beta_7$ integrin. Pharmacokinetic studies in rats showed good oral availability (43%) and low clearance (17 ml/kg/min). Potentially useful for the treatment of inflammatory diseases including asthma rheumatoid arthritis, multiple sclerosis and inflammatory bowel disease. Other related compounds are:



Compound	R1	Formula
318574	Et	C ₂₂ H ₂₄ Cl ₂ N ₂ O ₆ S
318575	cyclopropyl	C ₂₃ H ₂₄ Cl ₂ N ₂ O ₆ S

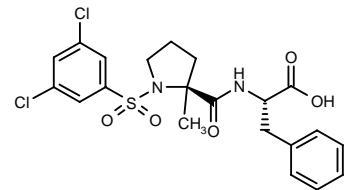
SOURCE – Merck & Co.

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1. Durette, P.L. et al. (Merck & Co., Inc.) *Substd. β -alanine derivs. as cell adhesion inhibitors.* WO 0071572.
2. Lin, L.S. et al. *The discovery of acylated β -amino acids as potent and orally bioavailable VLA-4 antagonists.* Bioorg Med Chem Lett 2002, 12(4): 611.

318580

N-(3,5-Dichlorophenylsulfonyl)-2-methyl-L-prolyl-L-phenylalanine



C21 H22 Cl2 N2 O5 S; Mol wt: 485.3858

ACTION – Potent and selective VLA-4 ($\alpha_4\beta_1$ integrin) antagonist ($IC_{50} = 1$ nM) with high selectivity over $\alpha_4\beta_7$ integrin. Compound exhibited good pharmacokinetics in rats, dogs, rhesus monkeys and sheep, with an oral availability of 23-59% and low but sustained circulating drug levels. Potentially useful for the treatment of asthma, rheumatoid arthritis and multiple sclerosis.

SOURCE – Merck & Co.

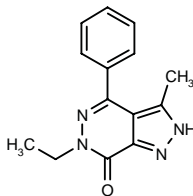
REFERENCES

1. Durette, P.L. et al. (Merck & Co., Inc.) *Heterocyclic amide cpds. as cell adhesion inhibitors*. EP 1001764, WO 9853814.
2. Kopka, I.E. et al. *Substituted N-(3,5-dichlorobenzenesulfonyl)-L-prolyl-phenylalanine analogues as potent VLA-4 antagonists*. Bioorg Med Chem Lett 2002, 12(4): 637.

CC-3

318914

6-Ethyl-3-methyl-4-phenyl-6,7-dihydro-2H-pyrazolo-[3,4-d]pyridazin-7-one



C14 H14 N4 O; Mol wt: 254.2916

ACTION – Potent phosphodiesterase type 4 (PDE4) inhibitor ($IC_{50} = 2$ μ M) with > 20-fold selectivity over PDE3 and lower affinity than rolipram for high-affinity rolipram binding sites ($IC_{50} = 10$ and 0.006 μ M, respectively). Compound exhibited *in vitro* relaxant and antiinflammatory activities; it relaxed rat lung passively sensitized with ovalbumin ($IC_{50} = 2.7$ μ M) and inhibited lipopolysaccharide (LPS)-induced TNF- α production in human monocytes ($IC_{50} = 5.8$ μ M). Potentially useful as an antiasthmatic agent.

SOURCES – Università degli Studi di Firenze, Firenze (IT); Forschungszentrum Borstel, Borstel (DE).

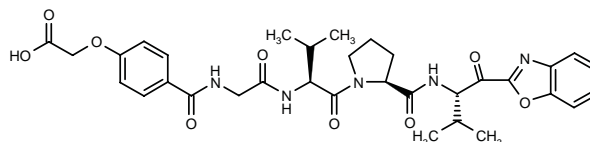
REFERENCES

1. Dal Piaz, V. et al. *Novel heterocyclic-fused pyridazinones as potent and selective phosphodiesterase IV inhibitors*. J Med Chem 1997, 40(10): 1417.
2. Martin, C. et al. *Airway relaxant and anti-inflammatory properties of a PDE4 inhibitor with low affinity for the high-affinity rolipram binding site*. 98th Int Conf Am Thorac Soc (May 17-22, Atlanta) 2002, Abst C29.
3. Martin, C. et al. *Airway relaxant and anti-inflammatory properties of a PDE4 inhibitor with low affinity for the high-affinity rolipram binding site*. Naunyn-Schmied Arch Pharmacol 2002, 365(4): 284.

AGENTS FOR RESPIRATORY DISTRESS SYNDROME

318551

2-[N-[4-(Carboxymethoxy)benzoyl]glycyl-L-valyl-L-prolyl-L-valyl]benzoxazole



C33 H39 N5 O9; Mol wt: 649.6971

ACTION – Human neutrophil elastase (HNE) inhibitor ($IC_{50} = 33$ nM) able to almost completely inhibit HNE-induced lung hemorrhage in hamsters after i.v. bolus administration of 30 mg/kg. Potentially useful for the treatment of acute respiratory distress syndrome.

SOURCE – Dainippon Pharmaceutical.

REFERENCES

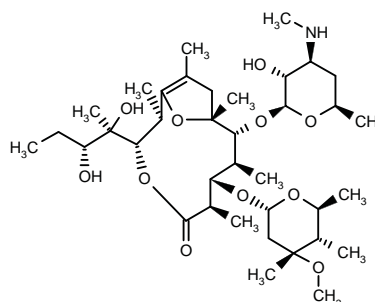
1. Sato, F. et al. *Design and synthesis of peptide-based carboxylic acid-containing transition-state inhibitors of human neutrophil elastase*. Bioorg Med Chem Lett 2002, 12(4): 551.

TREATMENT OF CYSTIC FIBROSIS

EM-703

317957

3(R)-[1(R),2(R)-Dihydroxy-1-methylbutyl]-9(R)-[3(R)-hydroxy-6(R)-methyl-4(S)-(methylamino)tetrahydropyran-2(S)-yloxy]-7(S)-[4-methoxy-4(R),5(S),6(S)-trimethyl-tetrahydropyran-2(S)-yloxy]-2(R),6(R),8(S),10(R),12-pentamethyl-4,13-dioxabicyclo[8.2.1]tridec-1(12)-en-5-one



C37 H65 N O11; Mol wt: 699.9165

ACTION – A pseudoerythromycin derivative with reduced antibacterial activity and potential as an antiinflammatory agent. It was shown to promote differentiation of human monocytes to macrophages with an EC₅₀ of 0.3 µM. Compound was effective in a mouse model of pulmonary fibrosis following oral administration at 50 mg/kg/day for 17 days. In a mouse model of influenza-induced pneumonia, EM-703 was able to increase survival rates at 0.3 mg/kg i.p., but was ineffective at 0.03 mg/kg.

SOURCE – Kitasato Institute, Tokyo (JP).

REFERENCES

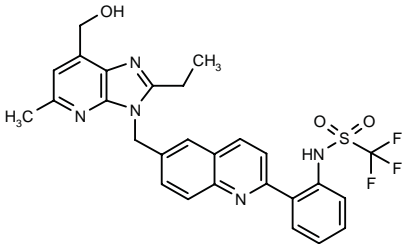
1. Omura, S. et al. (Kitasato Institute) *Novel pseudoerythromycin derivs.* WO 0214338.

CARDIOVASCULAR DRUGS

ANTIHYPERTENSIVE DRUGS

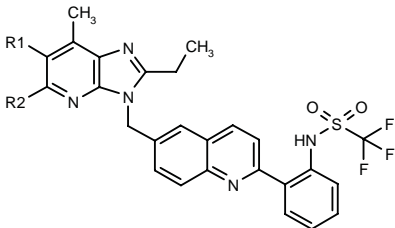
317215

N-[2-[6-[2-Ethyl-7-(hydroxymethyl)-5-methyl-3*H*-imidazo[4,5-*b*]pyridin-3-ylmethyl]quinolin-2-yl]phenyl]trifluoromethanesulfonamide



C27 H24 F3 N5 O3 S; Mol wt: 555.5786

ACTION – Angiotensin II antagonist (IC₅₀ = 17 nM) with *in vivo* activity in rat models of pulmonary hypertension following i.v. administration. Potentially useful for the treatment of hypertension, pulmonary hypertension, cardiopathies including angina pectoris, arrhythmia and myocardial infarction, obesity, cerebrovascular diseases, senile dementia and ophthalmopathies such as glaucoma. Other exemplified quinoline derivatives are:



Compound	R1	R2	Formula
317216	H	CH2OH	C ₂₇ H ₂₄ F ₃ N ₅ O ₃ S
317217	OH	Me	C ₂₇ H ₂₄ F ₃ N ₅ O ₃ S

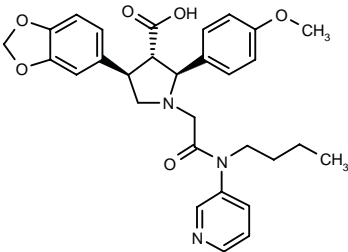
SOURCES – Asahi Glass; Mitsubishi Pharma.

REFERENCES

1. Takebe, Y. et al. (Asahi Glass Co., Ltd.;Mitsubishi Pharma Corp.) *Quinoline derivs. and medicinal compsns. containing them.* JP 2002030085.

318243

(2*S**,3*S**,4*R**)-4-(1,3-Benzodioxol-5-yl)-1-[*N*-butyl-*N*-(3-pyridyl)carbamoylmethyl]-2-(4-methoxyphenyl)pyrrolidine-3-carboxylic acid



C30 H33 N3 O6; Mol wt: 531.6057

ACTION – A representative compound from a series of substituted pyrrolidine derivatives that act as endothelin receptor antagonists. Compound gave an IC₅₀ of 0.71 nM against human ET_A receptors and exhibited 1,200-fold selectivity over ET_B receptors. Also, it showed 92% binding to plasma proteins. Potentially useful for the treatment of hypertension, pulmonary hypertension, Raynaud’s disease, congestive heart failure, myocardial ischemia, reperfusion injury, coronary angina, cerebral ischemia, cerebral vasospasm, acute and chronic renal failure, nonsteroidal antiinflammatory drug-induced gastric ulceration, ciclosporin-induced nephrotoxicity, asthma, adult respiratory distress syndrome, lupus erythematosus, retinopathies, psoriasis, systemic sclerosis, cirrhosis, prostatic and cardiac hyperplasia, restenosis, atherosclerosis, thrombosis, cancer and nociception.

SOURCE – Abbott.

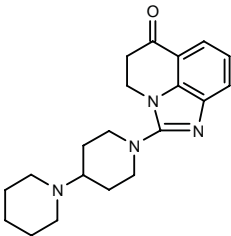
REFERENCES

1. Winn, M. et al. (Abbott Laboratories Inc.) *Endothelin antagonists.* WO 0217912.

TREATMENT OF DISORDERS OF THE CORONARY ARTERIES AND ATHEROSCLEROSIS

317194

2-(1,4'-Bipiperidin-1'-yl)-5,6-dihydro-4*H*-imidazo[4,5,1-*ij*]-quinolin-6-one



C20 H26 N4 O; Mol wt: 338.4524

ACTION – A pseudoerythromycin derivative with reduced antibacterial activity and potential as an antiinflammatory agent. It was shown to promote differentiation of human monocytes to macrophages with an EC₅₀ of 0.3 µM. Compound was effective in a mouse model of pulmonary fibrosis following oral administration at 50 mg/kg/day for 17 days. In a mouse model of influenza-induced pneumonia, EM-703 was able to increase survival rates at 0.3 mg/kg i.p., but was ineffective at 0.03 mg/kg.

SOURCE – Kitasato Institute, Tokyo (JP).

REFERENCES

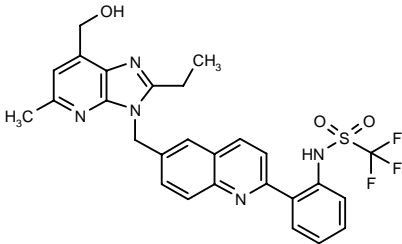
1. Omura, S. et al. (Kitasato Institute) *Novel pseudoerythromycin derivs.* WO 0214338.

CARDIOVASCULAR DRUGS

ANTIHYPERTENSIVE DRUGS

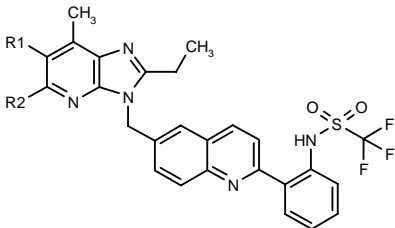
317215

N-[2-[6-[2-Ethyl-7-(hydroxymethyl)-5-methyl-3*H*-imidazo[4,5-*b*]pyridin-3-ylmethyl]quinolin-2-yl]phenyl]trifluoromethanesulfonamide



C27 H24 F3 N5 O3 S; Mol wt: 555.5786

ACTION – Angiotensin II antagonist (IC₅₀ = 17 nM) with *in vivo* activity in rat models of pulmonary hypertension following i.v. administration. Potentially useful for the treatment of hypertension, pulmonary hypertension, cardiopathies including angina pectoris, arrhythmia and myocardial infarction, obesity, cerebrovascular diseases, senile dementia and ophthalmopathies such as glaucoma. Other exemplified quinoline derivatives are:



Compound	R1	R2	Formula
317216	H	CH2OH	C ₂₇ H ₂₄ F ₃ N ₅ O ₃ S
317217	OH	Me	C ₂₇ H ₂₄ F ₃ N ₅ O ₃ S

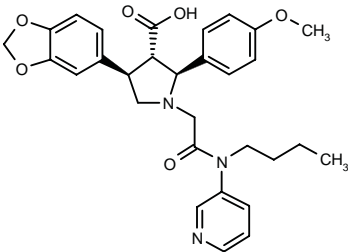
SOURCES – Asahi Glass; Mitsubishi Pharma.

REFERENCES

1. Takebe, Y. et al. (Asahi Glass Co., Ltd.;Mitsubishi Pharma Corp.) *Quinoline derivs. and medicinal compsns. containing them.* JP 2002030085.

318243

(2*S**,3*S**,4*R**)-4-(1,3-Benzodioxol-5-yl)-1-[*N*-butyl-*N*-(3-pyridyl)carbamoylmethyl]-2-(4-methoxyphenyl)pyrrolidine-3-carboxylic acid



C30 H33 N3 O6; Mol wt: 531.6057

ACTION – A representative compound from a series of substituted pyrrolidine derivatives that act as endothelin receptor antagonists. Compound gave an IC₅₀ of 0.71 nM against human ET_A receptors and exhibited 1,200-fold selectivity over ET_B receptors. Also, it showed 92% binding to plasma proteins. Potentially useful for the treatment of hypertension, pulmonary hypertension, Raynaud’s disease, congestive heart failure, myocardial ischemia, reperfusion injury, coronary angina, cerebral ischemia, cerebral vasospasm, acute and chronic renal failure, nonsteroidal antiinflammatory drug-induced gastric ulceration, ciclosporin-induced nephrotoxicity, asthma, adult respiratory distress syndrome, lupus erythematosus, retinopathies, psoriasis, systemic sclerosis, cirrhosis, prostatic and cardiac hyperplasia, restenosis, atherosclerosis, thrombosis, cancer and nociception.

SOURCE – Abbott.

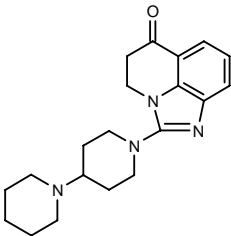
REFERENCES

1. Winn, M. et al. (Abbott Laboratories Inc.) *Endothelin antagonists.* WO 0217912.

TREATMENT OF DISORDERS OF THE CORONARY ARTERIES AND ATHEROSCLEROSIS

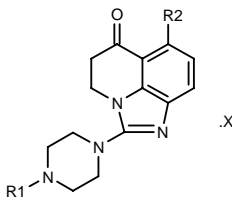
317194

2-(1,4'-Bipiperidin-1'-yl)-5,6-dihydro-4*H*-imidazo[4,5,1-*ij*]-quinolin-6-one

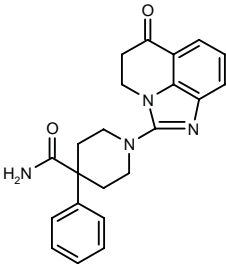


C20 H26 N4 O; Mol wt: 338.4524

ACTION – Agent with the ability to inhibit poly(ADP-ribose)polymerase (PARP, NAD⁺ ADP-ribosyltransferase), potentially useful for the treatment of myocardial infarction, cardiac ischemia, cardiac insufficiency, atherosclerosis, post-PTCA restenosis, cerebral ischemia, thromboembolic trauma, neurodegenerative diseases such as Parkinson’s disease, Alzheimer’s disease and Huntington’s chorea, acute renal insufficiency, transplant rejection, inflammatory, immune and autoimmune disorders, rheumatism, pancreatitis, septic shock, respiratory distress syndrome, cancer, AIDS, hepatitis, psoriasis, vasculitis, ulcerative colitis, multiple sclerosis and myasthenia. Other exemplified benzimidazole derivatives include the following:



Compound	R1	R2	X	Formula
317195	4-N(Me)2-Ph	H		C ₂₂ H ₂₅ N ₅ O
317196	4-NH2-Ph	H	2HCl	C ₂₀ H ₂₁ N ₅ O.2HCl
317197	Pr	H	2HCl	C ₁₇ H ₂₂ N ₄ O.2HCl
317198	H	H	2HCl	C ₁₄ H ₁₆ N ₄ O.2HCl
317199	4-Pyr	H	2HCl	C ₁₉ H ₁₉ N ₅ O.2HCl
317201	4-OH-Ph	H		C ₂₀ H ₂₀ N ₄ O ₂
317202	4-F-Ph	Me		C ₂₁ H ₂₁ FN ₄ O



317200: C22 H22 N4 O2

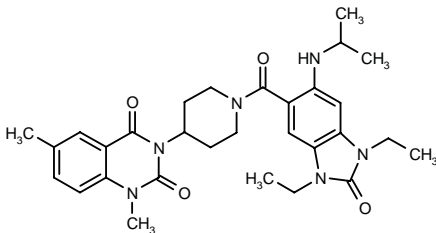
SOURCE – Sanofi-Synthélabo.

REFERENCES

1. Barth, F. et al. (Sanofi-Synthélabo) *Benzimidazole derivs., preparation and therapeutic use thereof*. WO 0212239.

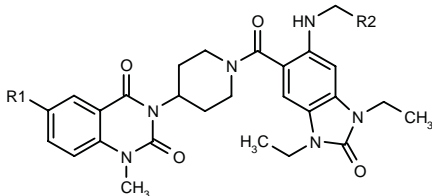
317623

3-[1-[1,3-Diethyl-6-(isopropylamino)-2-oxo-2,3-dihydro-1H-benzimidazol-5-ylcarbonyl]piperidin-4-yl]-1,6-dimethylquinazoline-2,4(1H,3H)-dione



C30 H38 N6 O4; Mol wt: 546.6682

ACTION – Adenosine uptake inhibitor that inhibited [³H]-NBI binding to pig renal cortex preparations by 92% at 1 μM, and also prevented the uptake of [³H]-adenosine by human erythrocytes with an IC₅₀ of 0.56 nM. Potentially useful as a cardioprotective agent, as well as in the treatment of cerebral ischemia, renal diseases such as nephritis and diabetic retinopathy, pancreatitis and spasm. Other related compounds are:



Compound	R1	R2	Formula
317624	Me	Me	C ₂₉ H ₃₆ N ₆ O ₄
317626	Me	CH2OH	C ₂₉ H ₃₆ N ₆ O ₅
317627	Cl	H	C ₂₇ H ₃₁ ClN ₆ O ₄

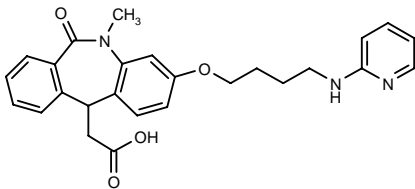
SOURCE – Kyowa Hakko.

REFERENCES

1. Sashou, S. et al. (Kyowa Hakko Kogyo Co., Ltd.) *Aromatic cpds*. JP 2002047287.

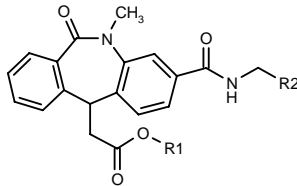
317795

2-[5-Methyl-6-oxo-3-[4-(pyridin-2-ylamino)butoxy]-6,11-dihydro-5H-dibenzo[b,e]azepin-11-yl]acetic acid

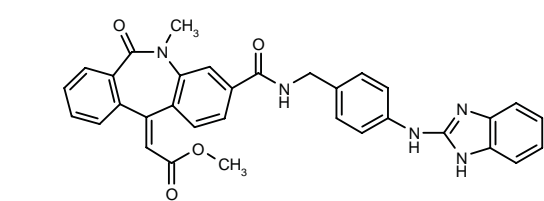


C26 H27 N3 O4; Mol wt: 445.5163

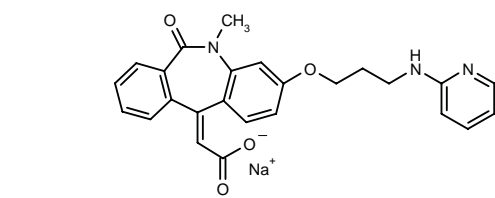
ACTION – Agent with affinity for α_vβ₃ (vitronectin) receptors and potential in the treatment of thrombosis, myocardial infarction, stroke, congestive heart failure, restenosis, diabetic angiopathy, atherosclerosis, cancer, osteoporosis, rheumatoid arthritis and for wound healing, among other α_vβ₃-related disorders. Other exemplified diarylazepine derivatives are:



Compound	R1	R2	Formula
317800	Na	4-(2-benzimidazolyl-NH)-Ph	C ₃₂ H ₂₆ N ₅ NaO ₄
317804	Na	2-benzimidazolyl	C ₂₆ H ₂₁ N ₄ NaO ₄
317805	Na	5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl-(CH2)3	C ₃₀ H ₃₁ N ₄ NaO ₄
317806	H	4-(2-benzimidazolyl-NH)-cyclohexyl	C ₃₂ H ₃₃ N ₅ O ₄
317807	H	5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl-(CH2)4	C ₃₁ H ₃₄ N ₄ O ₄
317808	H	2-benzimidazolyl-NH(CH2)3	C ₂₉ H ₂₉ N ₅ O ₄



317802: C33 H27 N5 O4



317803: C25 H22 N3 Na O4

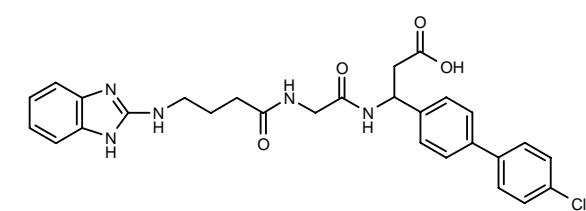
SOURCE – BASF (Abbott).

REFERENCES

1. Geneste, H. et al. (BASF AG) *Novel subst. diaryl azepine derivs. as integrin ligands.* DE 10039998, WO 0214320.

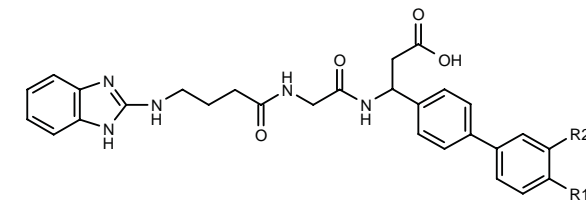
318056

3-[2-[4-(1*H*-Benzimidazol-2-ylamino)butyramido]-acetamido]-3-(4'-chlorobiphenyl-4-yl)propionic acid



C28 H28 Cl N5 O4; Mol wt: 534.0132

ACTION – An antagonist at $\alpha_v\beta_3$ (vitronectin) and $\alpha_v\beta_5$ integrin receptors. Potentially useful for the treatment of thrombosis, myocardial infarction, coronary heart disease, arteriosclerosis, inflammation, cancer, osteoporosis, infections, rheumatoid arthritis, diabetic retinopathy and postangioplasty restenosis. Other exemplified biphenyl derivatives are:



Compound	R1	R2	Formula
318058	F	Cl	C ₂₈ H ₂₇ ClFN ₅ O ₄
318059	H	F	C ₂₈ H ₂₆ FN ₅ O ₄

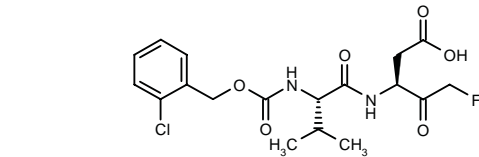
SOURCE – Merck KGaA.

REFERENCES

1. Stähle, W. et al. (Merck Patent GmbH) *Biphenyl derivs. and their use thereof as integrin inhibitors.* DE 10041423, WO 0216328.

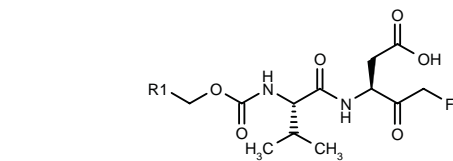
318063

N-(2-Chlorobenzoyloxycarbonyl)-L-valyl-L-aspartyl-fluoro-methane



C18 H22 Cl F N2 O6; Mol wt: 416.8308

ACTION – Caspase inhibitor giving an IC₅₀ of 36 nM against caspase 3. Potentially useful for the treatment of conditions associated with unwanted apoptosis. In particular, the compound is reportedly useful for the prevention of cell death in cardiac muscle resulting from myocardial infarction, congestive heart failure, cardiomyopathy and viral infection of the heart. Other exemplified compounds are:



Compound	R1	Formula
318064	3-Cl-Ph	C ₁₈ H ₂₂ ClFN ₂ O ₆
318066	CH2Ph	C ₁₉ H ₂₅ FN ₂ O ₆
318068	4-Cl-Ph	C ₁₈ H ₂₂ ClFN ₂ O ₆
318070	cyclohexyl	C ₁₈ H ₂₉ FN ₂ O ₆
318072	Me	C ₁₃ H ₂₁ FN ₂ O ₆

SOURCE – Cytovia (Maxim).

REFERENCES

1. Cai, S.X. et al. (Cytovia, Inc.) *Caspase inhibitors and the use thereof.* US 6355618.

NMI-1147/1165^{2,3}

318222

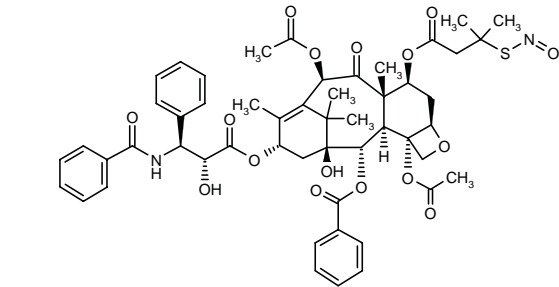
Combination of NMI-1147 (paclitaxel-SNO) and NMI-1165 (adamantyl-SNO)

NMI-1147^{1,3,4}

318156

7-*O*-[3-Methyl-3-(nitrososulfanyl)butyryl]paclitaxel

Paclitaxel-SNO



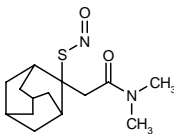
C52 H58 N2 O16 S ; Mol wt: 999.0942

NMI-1165³

318198

N,N-Dimethyl-2-[2-(nitrososulfanyl)adamant-2-yl]acetamide

Adamantyl-SNO



C14 H22 N2 O2 S ; Mol wt: 282.4058

ACTION – Nitrosylated paclitaxel (NMI-1147) and nitric oxide (NO) donor (NMI-1165) combination for use in coating stents for the prevention of restenosis after angioplasty. In a 28-day model of restenosis in rabbits, the combination produced a significant reduction in stenosis compared with paclitaxel alone.

SOURCES – Brigham & Women’s Hospital, Boston, MA (US); Cordis; NitroMed.

REFERENCES

1. Garvey, D.S. et al. (NitroMed Inc.) *Nitrosated and nitrosylated taxanes, compsns. and methods of use.* WO 0198286.

2. Stamler, J.S. et al. (NitroMed Inc.;Brigham & Women’s Hospital) *Localized use of nitric oxide-adducts to prevent internal tissue damage.* US 6087479.

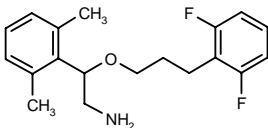
3. Lin, C.-E. et al. *Design and synthesis of nitrosylated paclitaxel (NO-paclitaxel) and adamantanyl nitric oxide donor as antirestenosis agents.* 223rd ACS Natl Meet (April 7-11, Orlando) 2002, Abst MEDI 36.

4. Young, D.V. et al. *Nitrosylation of synthetic taxol derivatives confers antiplatelet functionality while retaining antiproliferative activity.* Mol Biol Cell 2000, 11(Suppl.): 232a.

ANTIARRHYTHMIC DRUGS

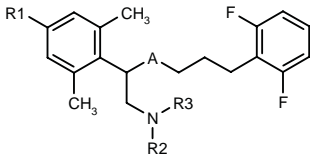
318087

2-[3-(2,6-Difluorophenyl)propoxy]-2-(2,6-dimethylphenyl)-ethylamine

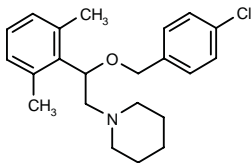


C19 H23 F2 N O; Mol wt: 319.3927

ACTION – Voltage-dependent sodium channel blocker considered to have potential in the treatment of arrhythmia, spasms, myocardial and brain ischemia, epilepsy, hypoglycemia, hypoxia, anoxia, brain trauma, brain edema, perinatal asphyxia, cerebellar degeneration, amyotrophic lateral sclerosis, Huntington’s disease, Alzheimer’s disease, Parkinson’s disease, manic depressive psychosis, hypotonia, myocardial infarction, angina pectoris, chronic and neuropathic pain, and also as a local anesthetic agent. Other exemplified phenyl-substituted ethanamines include the following:



Compound	R1	R2	R3	A	Formula
318088	H	Me	cyclopropyl-CH2	-O-	C ₂₄ H ₃₁ F ₂ NO
318089	H	Et	Et	-O-	C ₂₃ H ₃₁ F ₂ NO
318090	H	H	CH2CH2CF3	-O-	C ₂₂ H ₂₆ F ₃ NO
318092	H		-(CH2)4-	-(i-BuCH2)N-	C ₂₈ H ₄₀ F ₂ N ₂
318093	Me		-(CH2)5-	-O-	C ₂₅ H ₃₃ F ₂ NO
318094	H	Et	CH2CH(Me)Et	-O-	C ₂₆ H ₃₇ F ₂ NO
318096	H	H	(CH2)3Ph	-O-	C ₂₈ H ₃₃ F ₂ NO



318091: C22 H28 Cl N O

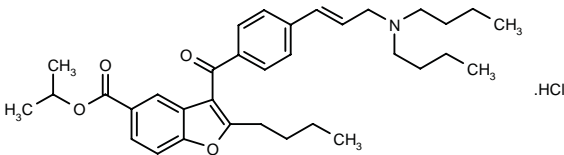
SOURCE – Boehringer Ingelheim.

REFERENCES

1. Fuchs, K. et al. (Boehringer Ingelheim Pharma KG) *Phenyl- and phenylalkyl-substd. ethanolamines and ethylenediamines.* DE 10040901, WO 0216308.

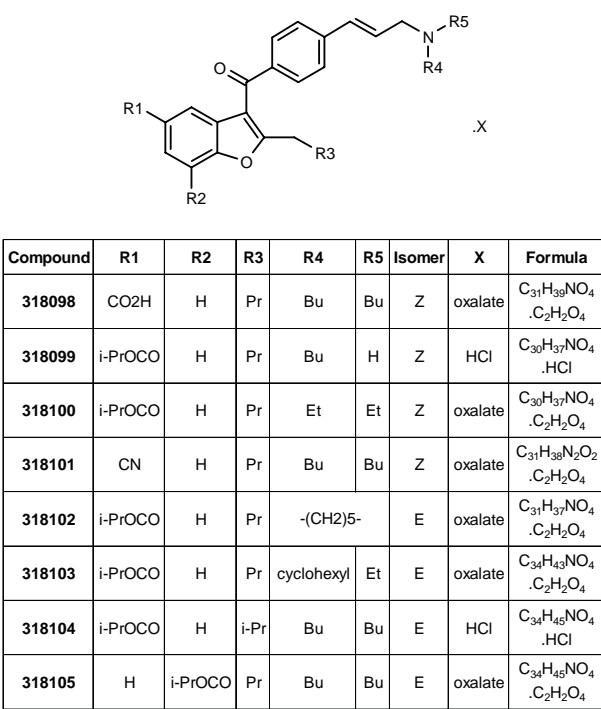
318097

2-Butyl-3-[4-[3-(dibutylamino)-1(E)-propenyl]benzoyl]-1-benzofuran-5-carboxylic acid isopropyl ester hydrochloride



C34 H45 N O4 . HCl; Mol wt: 568.1934

ACTION – Antiarrhythmic agent reported to have antiadrenergic and antioxidant properties, as well as affinity for σ receptors, nitric oxide (NO) synthesis-promoting effects and/or angiotensin II-, arginine-, vasopressin-, neuropeptide Y- and endothelin-inhibitory activity. Potentially useful for the treatment of arrhythmia, angina pectoris, hypertension, cerebral circulatory insufficiency, cardiac insufficiency and myocardial infarction. Other exemplified compounds are:



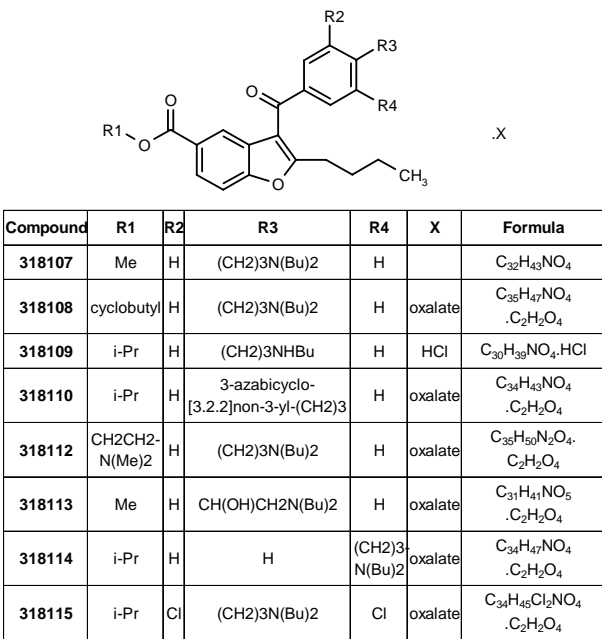
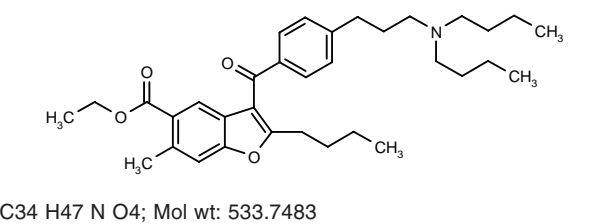
SOURCE – Sanofi-Synthélabo.

REFERENCES

1. Assens, J.-L. et al. (Sanofi-Synthélabo) *Aminoalkenylbenzoyl-benzofuran or benzothiophene derivs., method for preparing same and compsns. containing same.* FR 2813307, WO 0216338.

318106

2-Butyl-3-[4-[3-(dibutylamino)propyl]benzoyl]-6-methyl-1-benzofuran-5-carboxylic acid ethyl ester



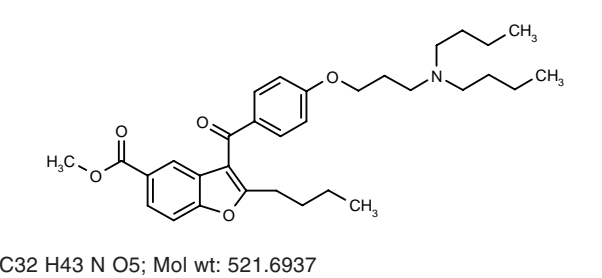
SOURCE – Sanofi-Synthélabo.

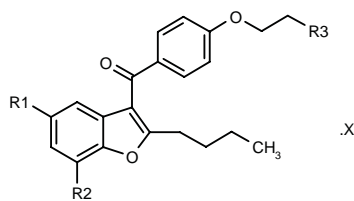
REFERENCES

1. Assens, J.-L. et al. (Sanofi-Synthélabo) *Aminoalkylbenzoyl-benzofuran or benzothiophene derivs., method for preparing same and compsns. containing same.* FR 2813306, WO 0216339.

318116

2-Butyl-3-[4-[3-(dibutylamino)propoxy]benzoyl]-1-benzofuran-5-carboxylic acid methyl ester





Compound	R1	R2	R3	X	Formula
318117	CONHCH2-CH2CO2H	H	CH2N(Bu)2		C ₃₄ H ₄₆ N ₂ O ₆
318119	CO2Me	H	4-NO2-Ph-CH2CH2N(Me)		C ₃₂ H ₃₄ N ₂ O ₇
318120	i-BuOCO	H	CH2N(Bu)2	oxalate	C ₃₅ H ₄₉ NO ₅ ·C ₂ H ₂ O ₄
318121	CO2Me	H	4-Me-1-Piz-CH2		C ₂₉ H ₃₆ N ₂ O ₅
318122	CO2Me	H	cyclohexyl-N(Et)CH2	oxalate	C ₃₂ H ₄₁ NO ₅ ·C ₂ H ₂ O ₄
318123	i-PrOCO	H	4-OH-1-Pip-CH2	oxalate	C ₃₁ H ₃₉ NO ₆ ·C ₂ H ₂ O ₄
318124	CO2H	H	CH2N(cyclohexyl)2	HCl	C ₃₅ H ₄₅ NO ₅ ·HCl
318125	H	CO2Me	cis-3,5-(Me)2-1-Pip-CH2	HCl	C ₃₁ H ₃₉ NO ₅ ·HCl

SOURCE – Sanofi-Synthélabo.

REFERENCES

1. Assens, J.-L. et al. (Sanofi-Synthélabo) *Aminoalkoxybenzoyl-benzofuran or benzothiophene derivs., method for preparing same and compsns. containing same.* FR 2813308, WO 0216340.

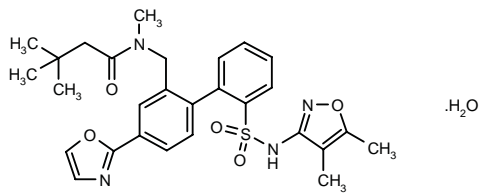
HEART FAILURE THERAPY

EDONENTAN*

272888

N-[2'-(4,5-Dimethylisoxazol-3-yl)sulfamoyl]-4-(2-oxazolyl)biphenyl-2-ylmethyl]-N,3,3-trimethylbutyramide hydrate

BMS-207940-02



C28 H32 N4 O5 S . H2O; Mol wt: 554.6646

ACTION – Potent, selective and orally available endothelin ET_A receptor antagonist, a derivative of BMS-193884 with improved affinity and absorption. Currently in phase II clinical trials for heart failure.

SOURCE – Bristol-Myers Squibb.

REFERENCES

- 1. Bird, J.E. (Bristol-Myers Squibb Co.) *Method for preventing or treating low renin hypertension by administering an endothelin antagonist.* WO 9833781.
- 2. Murugesan, N. et al. (Bristol-Myers Squibb Co.) *Endothelin antagonists: N-[[2'-[[4,5-dimethyl-3-isoxazolyl]amino]sulfonyl]-4-(2-oxazolyl) [1,1'-biphenyl]-2-yl]methyl]-N,3,3-trimethylbutanamide N-(4,5-dimethyl-3-isoxazolyl)-2'-[[3,3-dimethyl-2-oxo-1-pyrrolidinyl)methyl]-4'-(2-oxazolyl)[1,1'-biphenyl]-2-sulfonamide and salts thereof.* EP 0996618, US 6043265, WO 9833780.
- 3. Rajfer, S.I. (Bristol-Myers Squibb Co.) *Method for preventing or treating erectile dysfunction by administering an endothelin antagonist.* WO 9910345.
- 4. Murugesan, N. et al. *Biphenylsulfonamido endothelin A receptor antagonists: Discovery and SAR of potent, selective and orally active second generation antagonists.* 223rd ACS Natl Meet (April 7-11, Orlando) 2002, Abst MEDI 120.

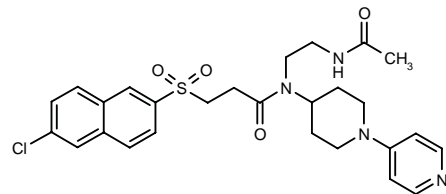
*Identified compound **272888** Drug Data Rep 1999, 021(03): 0221.

AGENTS AFFECTING BLOOD COAGULATION

ANTICOAGULANTS

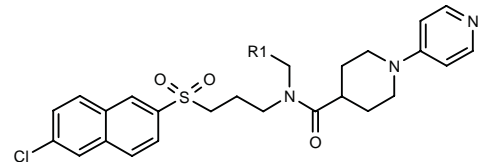
317018

N-(2-Acetamidoethyl)-3-(6-chloronaphthalen-2-yl-sulfonyl)-N-[1-(4-pyridyl)piperidin-4-yl]propionamide

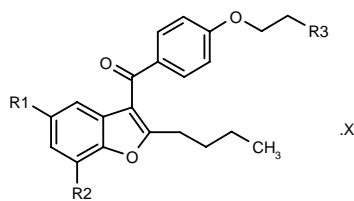


C27 H31 Cl N4 O4 S; Mol wt: 543.0849

ACTION – Anticoagulant, a factor Xa inhibitor (IC₅₀ = 39 nM) for use in the treatment of arterial and venous thromboobstructive disease, inflammation, cancer, myocardial infarction, cerebral thrombosis, deep venous thrombosis, pulmonary thromboembolism and post-operative thromboembolism. Other exemplified sulfone derivatives are:



Compound	R1	Formula
317019	H	C ₂₅ H ₂₈ ClN ₃ O ₃ S
317020	CO2Me	C ₂₇ H ₃₀ ClN ₃ O ₅ S



Compound	R1	R2	R3	X	Formula
318117	CONHCH2-CH2CO2H	H	CH2N(Bu)2		C ₃₄ H ₄₆ N ₂ O ₆
318119	CO2Me	H	4-NO2-Ph-CH2CH2N(Me)		C ₃₂ H ₃₄ N ₂ O ₇
318120	i-BuOCO	H	CH2N(Bu)2	oxalate	C ₃₅ H ₄₉ NO ₅ ·C ₂ H ₂ O ₄
318121	CO2Me	H	4-Me-1-Piz-CH2		C ₂₉ H ₃₆ N ₂ O ₅
318122	CO2Me	H	cyclohexyl-N(Et)CH2	oxalate	C ₃₂ H ₄₁ NO ₅ ·C ₂ H ₂ O ₄
318123	i-PrOCO	H	4-OH-1-Pip-CH2	oxalate	C ₃₁ H ₃₉ NO ₆ ·C ₂ H ₂ O ₄
318124	CO2H	H	CH2N(cyclohexyl)2	HCl	C ₃₅ H ₄₅ NO ₅ ·HCl
318125	H	CO2Me	cis-3,5-(Me)2-1-Pip-CH2	HCl	C ₃₁ H ₃₉ NO ₅ ·HCl

SOURCE – Sanofi-Synthélabo.

REFERENCES

1. Assens, J.-L. et al. (Sanofi-Synthélabo) *Aminoalkoxybenzoyl-benzofuran or benzothiophene derivs., method for preparing same and compsns. containing same.* FR 2813308, WO 0216340.

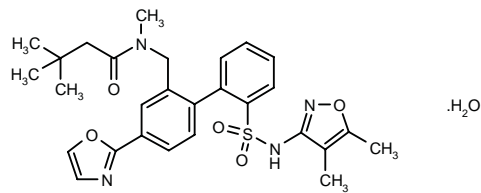
HEART FAILURE THERAPY

EDONENTAN*

272888

N-[2'-(4,5-Dimethylisoxazol-3-yl)sulfamoyl]-4-(2-oxazolyl)biphenyl-2-ylmethyl]-N,3,3-trimethylbutyramide hydrate

BMS-207940-02



C28 H32 N4 O5 S . H2O; Mol wt: 554.6646

ACTION – Potent, selective and orally available endothelin ET_A receptor antagonist, a derivative of BMS-193884 with improved affinity and absorption. Currently in phase II clinical trials for heart failure.

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3. Rajfer, S.I. (Bristol-Myers Squibb Co.) *Method for preventing or treating erectile dysfunction by administering an endothelin antagonist.* WO 9910345.
4. Murugesan, N. et al. *Biphenylsulfonamido endothelin A receptor antagonists: Discovery and SAR of potent, selective and orally active second generation antagonists.* 223rd ACS Natl Meet (April 7-11, Orlando) 2002, Abst MEDI 120.

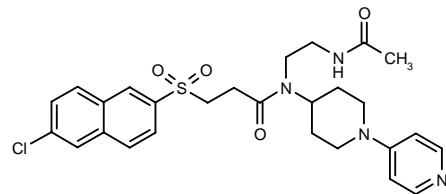
*Identified compound **272888** Drug Data Rep 1999, 021(03): 0221.

AGENTS AFFECTING BLOOD COAGULATION

ANTICOAGULANTS

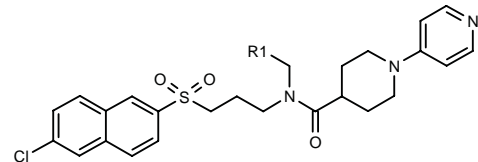
317018

N-(2-Acetamidoethyl)-3-(6-chloronaphthalen-2-yl-sulfonyl)-N-[1-(4-pyridyl)piperidin-4-yl]propionamide

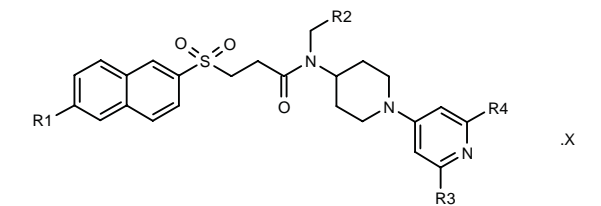


C27 H31 Cl N4 O4 S; Mol wt: 543.0849

ACTION – Anticoagulant, a factor Xa inhibitor (IC₅₀ = 39 nM) for use in the treatment of arterial and venous thromboobstructive disease, inflammation, cancer, myocardial infarction, cerebral thrombosis, deep venous thrombosis, pulmonary thromboembolism and post-operative thromboembolism. Other exemplified sulfone derivatives are:



Compound	R1	Formula
317019	H	C ₂₅ H ₂₈ ClN ₃ O ₃ S
317020	CO2Me	C ₂₇ H ₃₀ ClN ₃ O ₅ S



Compound	R1	R2	R3	R4	X	Formula
317022	Cl	H	H	H		C ₂₄ H ₂₆ ClN ₃ O ₃ S
317024	Cl	CO ₂ Et	H	H		C ₂₇ H ₃₀ ClN ₃ O ₅ S
317027	Cl	CH ₂ CO ₂ Et	H	H		C ₂₈ H ₃₂ ClN ₃ O ₅ S
317036	Cl	H	Me	H		C ₂₅ H ₂₈ ClN ₃ O ₃ S
317037	Cl	CH ₂ NHAc	Me	H		C ₂₈ H ₃₃ ClN ₄ O ₄ S
317038	Cl	CH ₂ NH ₂	Me	H	2C ₂ HF ₃ O ₂	C ₂₆ H ₃₁ ClN ₄ O ₃ S .2C ₂ HF ₃ O ₂
317039	Cl	CH ₂ NHSO ₂ Me	H	H		C ₂₆ H ₃₁ ClN ₄ O ₅ S ₂
317040	Br	H	Me	H		C ₂₅ H ₂₈ BrN ₃ O ₃ S
317041	Cl	CH ₂ CO ₂ Et	Me	H		C ₂₉ H ₃₄ ClN ₃ O ₅ S
317042	Cl	1-oxo-4-thiomorpholinyl -COCH ₂	Me	H		C ₃₁ H ₃₇ ClN ₄ O ₅ S ₂
317043	Cl	CH ₂ N(Me)Ac	Me	H		C ₂₉ H ₃₅ ClN ₄ O ₄ S
317044	Cl	H	Me	Me		C ₂₆ H ₃₀ ClN ₃ O ₃ S
317045	Cl	2-Pyr	Me	H		C ₃₀ H ₃₁ ClN ₄ O ₃ S

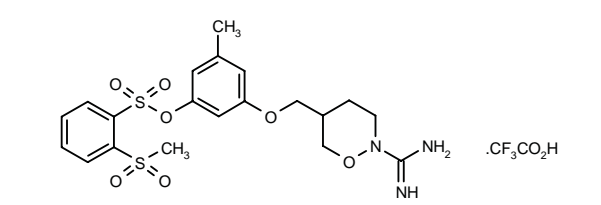
SOURCE – Takeda.

REFERENCES

1. Kubo, K. et al. (Takeda Chemical Industries, Ltd.) *Sulfone derivs., process for their production and use thereof*. WO 0206234.

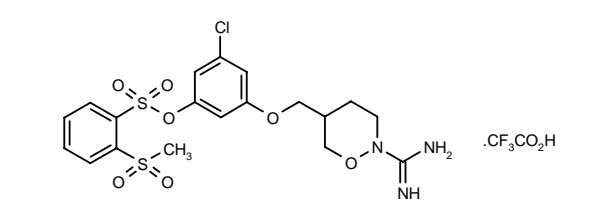
317111

2-(Methylsulfonyl)benzenesulfonic acid 3-(2-amidino-perhydro-1,2-oxazin-5-ylmethoxy)-5-methylphenyl ester trifluoroacetate

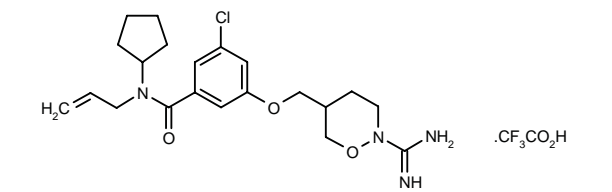


C₂₀ H₂₅ N₃ O₇ S₂ . C₂ H F₃ O₂; Mol wt: 597.5854

ACTION – An inhibitor of trypsin-like serine proteases, particularly thrombin ($K_i = 7$ nM). Potentially useful as an anticoagulant in the treatment of pancreatitis, thrombosis, ischemia, stroke, restenosis, emphysema and inflammation. Other exemplified cyclic oxyguanidine compounds are:



317112: C₁₉ H₂₂ Cl N₃ O₇ S₂ . C₂ H F₃ O₂



317113: C₂₁ H₂₉ Cl N₄ O₃ . C₂ H F₃ O₂

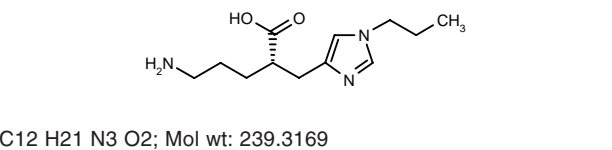
SOURCE – 3-Dimensional Pharmaceuticals.

REFERENCES

1. Wang, A. et al. (3-Dimensional Pharmaceuticals, Inc.) *Cyclic oxyguanidine protease inhibitors*. WO 0212207.

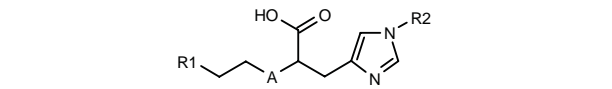
317472

(+)-5-Amino-2(S)-(1-propyl-1H-imidazol-4-ylmethyl)pentanoic acid



C₁₂ H₂₁ N₃ O₂; Mol wt: 239.3169

ACTION – An inhibitor of the activated form of thrombin-activatable fibrinolysis inhibitor (TAFIa), a 60-kDa glycoprotein found in human plasma and also known as procarboxypeptidase B, carboxypeptidase B, plasma carboxypeptidase B, carboxypeptidase U and carboxypeptidase R ($K_i = 13$ nM). TAFI is transformed during the blood coagulation process to the activated form, which acts on the fibrin matrix which comprises a developing blood clot to prevent its dissolution. By virtue of its activity, this compound is considered to have potential in the treatment of thrombosis, atherosclerosis, adhesions and dermal scarring, fibrotic conditions, inflammatory diseases and those conditions which benefit from maintaining or enhancing bradykinin levels in the body, such as hypertension, angina, heart failure, pulmonary hypertension and organ failure. Other exemplified substituted imidazoles include the following:



Compound	R1	R2	A	Isomer	Formula
317473	CH ₂ NH ₂	Pr	CH ₂		C ₁₃ H ₂₃ N ₃ O ₂
317474	NH ₂	H	NH	S	C ₈ H ₁₄ N ₄ O ₂
317475	NH ₂	5-thiazolyl-CH ₂	NH	S	C ₁₂ H ₁₇ N ₅ O ₂ S

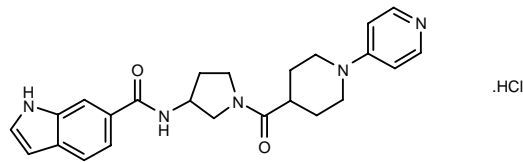
SOURCE – Pfizer.

REFERENCES

1. Allerton, C.M.N. et al. (Pfizer Ltd.;Pfizer Inc.) *Substd. imidazoles as TAFIa inhibitors*. WO 0214285.

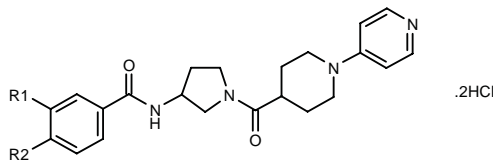
317492

N-[1-[1-(4-Pyridyl)piperidin-4-ylcarbonyl]pyrrolidin-3-yl]-1H-indole-6-carboxamide hydrochloride

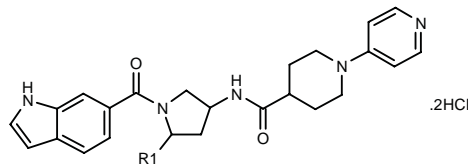


C24 H27 N5 O2 . HCl; Mol wt: 453.9712

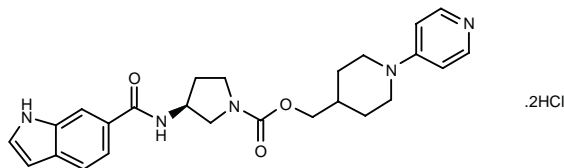
ACTION – Anticoagulant with the ability to inhibit factor Xa, potentially useful for the prophylaxis and treatment of thromboembolic disorders. Other exemplified compounds are:



Compound	R1,R2	Isomer	Formula
317493	-NHCH=CH-	S	C ₂₄ H ₂₇ N ₅ O ₂ .2HCl
317494	-NHCH=CH-	R	C ₂₄ H ₂₇ N ₅ O ₂ .2HCl
317496	-N=CHNH-		C ₂₃ H ₂₆ N ₆ O ₂ .2HCl



Compound	R1	Isomer	Formula
317498	H		C ₂₄ H ₂₇ N ₅ O ₂ .2HCl
317500	CO2H	2S,4S	C ₂₅ H ₂₇ N ₅ O ₄ .2HCl



317499: C25 H29 N5 O3 . 2HCl

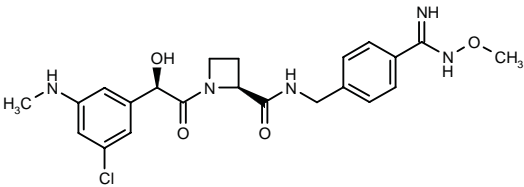
SOURCE – Lilly.

REFERENCES

1. Beight, D.W. et al. (Eli Lilly and Company) *Antithrombotic agents*. WO 0214308.

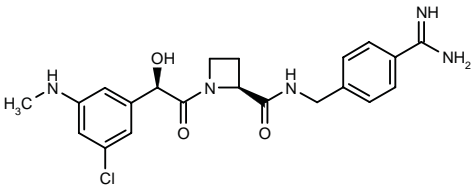
317579

1-[2(R)-[3-Chloro-5-(methylamino)phenyl]-2-hydroxy-acetyl]-N-[4-(N-methoxyamidino)benzyl]azetidine-2(S)-carboxamide



C22 H26 Cl N5 O4; Mol wt: 459.9314

ACTION – A prodrug of **317580**, a competitive inhibitor of trypsin-like proteases such as thrombin that is expected to be useful as an anticoagulant. This compound was found to exhibit good oral and parenteral bioavailability, and to be converted to the corresponding active thrombin inhibitor (free amidine) in human and rat liver microsomes. The free amidine exhibited an IC₅₀ for doubling the thrombin clotting time of < 0.02 μM and an IC₅₀ for doubling the activated partial thromboplastin time (APTT) of < 1 μM.



317580: C21 H24 Cl N5 O3

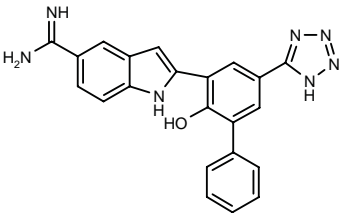
SOURCE – AstraZeneca.

REFERENCES

1. Inghardt, T. and Svensson, A. (AstraZeneca AB) *New amidino derivs. and their use as thrombin inhibitors*. WO 0214270.

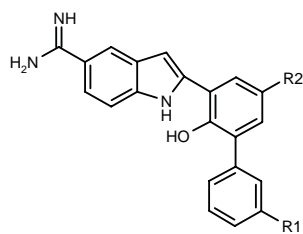
317688

2-[2-Hydroxy-5-(1H-tetrazol-5-yl)biphenyl-3-yl]-1H-indole-5-carboxamidine



C22 H17 N7 O; Mol wt: 395.4243

ACTION – Anticoagulant, a factor VIIa inhibitor with potential for the treatment of thromboembolic disorders including unstable angina, first or recurrent ischemic attack, stroke, atherosclerosis, venous thrombosis, deep vein thrombosis, thrombophlebitis, arterial embolism and kidney and pulmonary embolism. Other specifically claimed 2-phenylindole derivatives are:



Compound	R1	R2	Formula
317690	NO2	5-tetrazolyl	C ₂₂ H ₁₆ N ₈ O ₃
317691	NO2	5-tetrazolyl-CH2	C ₂₃ H ₁₈ N ₈ O ₃
317693	H	5-tetrazolyl-CH2	C ₂₃ H ₁₉ N ₇ O
317695	H	1,2,3-triazol-5-yl	C ₂₃ H ₁₈ N ₆ O
317698	H	1-tetrazolyl	C ₂₂ H ₁₇ N ₇ O

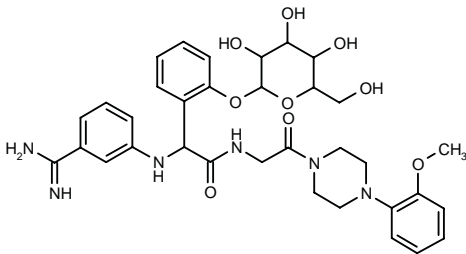
SOURCE – Celera Genomics.

REFERENCES

1. Leahy, E.M. (Celera Genomics) *Factor VIIa inhibitors*. WO 0214307.

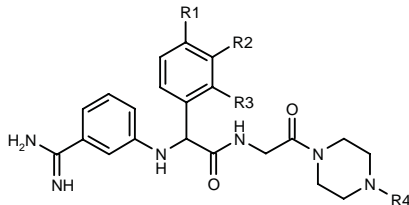
318076

2-(3-Amidinophenylamino)-2-[2-[6-(hydroxymethyl)-3,4,5-trihydroxyhydropyran-2-yloxy]phenyl]-N-[2-[4-(2-methoxyphenyl)piperazin-1-yl]-2-oxoethyl]acetamide



C34 H42 N6 O9; Mol wt: 678.7388

ACTION – Anticoagulant, a factor Xa inhibitor. Potentially useful for the treatment of thromboembolic disorders, arterial restenosis, blood poisoning, cancer and acute inflammatory disorders. Other exemplified compounds are:



Compound	R1	R2	R3	R4	Formula
318077	H	OCH2-CO2H	H	2,4-(F)2-Ph	C ₂₉ H ₃₀ F ₂ N ₆ O ₅
318078	H	H	H	2-NO2-Ph	C ₂₇ H ₂₉ N ₇ O ₄
318079	H	H	3,4,5-(OH)3-6-(CH2-OH)-THP-2-yl-O	4-Pyr	C ₃₂ H ₃₉ N ₇ O ₈
318080	H	H	OCH2CO2H	2-OH-Ph	C ₂₉ H ₃₂ N ₆ O ₆
318081	H	H	H	4-MeO-Ph	C ₂₈ H ₃₂ N ₆ O ₃
318082	OCH2Ph	OCH2-CO2H	H	2-MeO-Ph	C ₃₇ H ₄₀ N ₆ O ₇
318083	H	t-BuOCO-CH2O	H	2,4-(F)2-Ph	C ₃₃ H ₃₈ F ₂ N ₆ O ₅
318084	O(CH2)3-CO2H	H	OMe	2-MeO-Ph	C ₃₃ H ₄₀ N ₆ O ₇

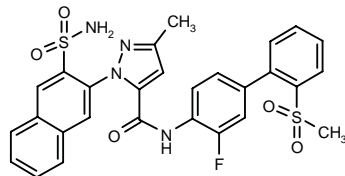
SOURCE – Morphochem.

REFERENCES

1. Cappi, M.W. et al. (Morphochem AG) *Novel cpds. inhibiting factor Xa activity*. DE 10041402, WO 0216312.

318263

N-[3-Fluoro-2'-(methylsulfonyl)biphenyl-4-yl]-3-methyl-1-(3-sulfamoylnaphthalen-2-yl)-1H-pyrazole-5-carboxamide



C28 H23 F N4 O5 S2; Mol wt: 578.6427

ACTION – Anticoagulant, a potent inhibitor of factor Xa with high selectivity over related proteases and an excellent oral pharmacokinetic profile.

SOURCE – Millennium.

REFERENCES

1. Zhu, B.-Y. et al. (COR Therapeutics, Inc.) *Benzamides and related inhibitors of factor Xa*. WO 0119788, WO 0119798.

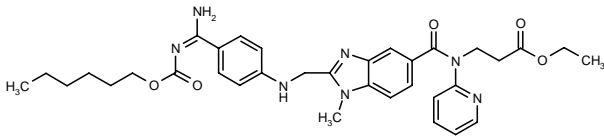
2. Zhu, B.-Y. et al. *Design, synthesis and structure-activity relationships of a series of novel and highly potent neutral inhibitors of factor Xa*. 223rd ACS Natl Meet (April 7-11, Orlando) 2002, Abst MEDI 126.

BIBR-1048^{1-5,7,8}

305702

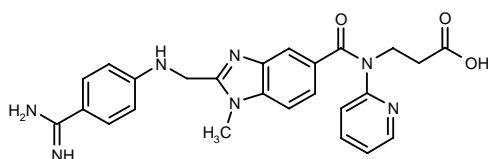
N-[2-[4-[N-(Hexyloxy-carbonyl)amidino]phenylaminomethyl]-1-methyl-1H-benzimidazol-5-ylcarbonyl]-N-(2-pyridyl)-β-alanine ethyl ester

BIBR-1048MS



C34 H41 N7 O5; Mol wt: 627.7419

ACTION – Anticoagulant, an orally active double prodrug of the potent and selective nonpeptide thrombin inhibitor **dabigatran** (K_i = 4.5 nM). In rabbits, compound (1-5 mg/kg p.o.) exhibited strong and long-lasting anti-coagulant activity measured as prolongation of activated partial thromboplastin time (aPTT) *ex vivo*. Selected for clinical development.



**Dabigatran [300695]¹⁻⁹: C₂₅ H₂₅ N₇ O₃
BIBR-953ZW**

SOURCE – Boehringer Ingelheim.

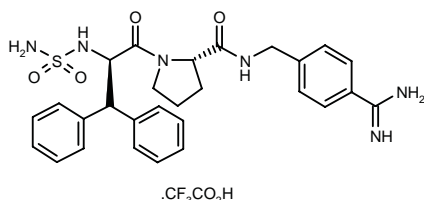
REFERENCES

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2. Busch, U. and Schmid, J. *Pharmacokinetics of the synthetic direct thrombin inhibitor BIBR 953ZW in different animal species*. Thromb Haemost 2001, (Suppl.): Abst P766.
3. Huel, N.H. et al. *Structure-based design of novel potent nonpeptide thrombin inhibitors*. J Med Chem 2002, 45(9): 1757.
4. Stangier, J. et al. *Pharmacokinetics of BIBR 953 ZW, a novel low molecular weight direct thrombin inhibitor in healthy volunteers*. Thromb Haemost 2001, (Suppl.): Abst OC2347.
5. Stassen, J.M. et al. *Ex vivo anticoagulant activity of BIBR953ZW, a novel synthetic direct thrombin inhibitor and of its prodrugs BIBR1048 MS in different animal species*. Thromb Haemost 2001, (Suppl.): Abst P763.
6. Stassen, J.M. et al. *Identification and in vitro characterization of BIBR 953 ZW, a novel synthetic low molecular weight direct thrombin inhibitor*. Thromb Haemost 2001, (Suppl.): Abst P775.
7. Stassen, J.M. et al. *Pharmacodynamics of the synthetic direct thrombin inhibitor BIBR953ZW in healthy subjects*. Thromb Haemost 2001, (Suppl.): Abst OC160.
8. Wienen, W. et al. *Effects of the direct thrombin inhibitor BIBR953ZW and its orally active prodrug BIBR 1048MS on experimentally-induced clot formation and template bleeding time in rats*. Thromb Haemost 2001, (Suppl.): Abst P761.
9. *Proposed international nonproprietary names (Prop. INN): List 83*. WHO Drug Inf 2000, 14(2): 112.

LB-30812

319213

N-Sulfamoyl-β-phenyl-D-phenylalanyl-L-proline N-(4-aminobenzyl)amide trifluoroacetate



C₂₈ H₃₂ N₆ O₄ S . C₂ H₃ F₃ O₂; Mol wt: 662.6867

ACTION – Potent and selective tripeptide thrombin inhibitor (K_i = 0.003 and 0.3 nM against human thrombin and bovine trypsin, respectively) with good oral absorption in rats and excellent antithrombotic activity in a rat model of venous thrombosis (100% inhibition at 1 mg/kg i.v.).

SOURCE – LG Chem.

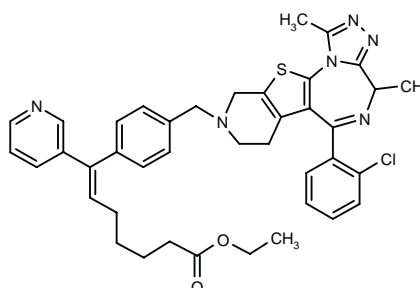
REFERENCES

1. Lee, K. et al. *Noncovalent tripeptidic thrombin inhibitors incorporating amidrazones, amine and amidine functions at P1*. Bioorg Med Chem Lett 2002, 12(7): 1017.

ANTIPLATELET THERAPY

317301

7-[4-[6-(2-Chlorophenyl)-1,4-dimethyl-7,8,9,10-tetrahydro-4H-pyrido[4',3':4,5]thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-9-ylmethyl]phenyl]-7-(3-pyridyl)-6(E/Z)-heptenoic acid ethyl ester



C₄₀ H₄₁ Cl N₆ O₂ S; Mol wt: 705.3229

ACTION – PAF antagonist and thromboxane synthase inhibitor (IC_{50} = 0.032 and 0.072 μ M, respectively) with excellent oral activity in mice and rats, giving ED_{50} values of 1.6 mg/kg p.o for protecting mice from the lethal effects of PAF and of 5.2 mg/kg p.o. for inhibiting serum TxB_2 production. Potentially useful for the treatment of ischemia, thrombosis, asthma and septic shock.

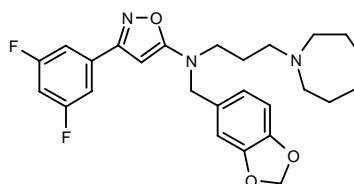
SOURCE – Nikken Chemicals.

REFERENCES

1. Fujita, M. et al. (Nikken Chemicals Co., Ltd.) *Triazolo-1,4-diazepine cpds. and medicinal compsn. containing the same*. EP 0995752, JP 1999071378, WO 9858930.
2. Fujita, M. et al. *Novel agents combining platelet activating factor (PAF) receptor antagonist with thromboxane synthase inhibitor (TxSI)*. Bioorg Med Chem Lett 2002, 12(5): 771.

317364

N-(1,3-Benzodioxol-5-ylmethyl)-3-(3,5-difluorophenyl)-N-[3-(perhydroazepin-1-yl)propyl]isoxazol-5-amine



C₂₆ H₂₉ F₂ N₃ O₃; Mol wt: 469.5291

ACTION – Nonpeptide, small-molecule antagonist of the human platelet thrombin receptor (PAR-1; IC_{50} = 0.21 μ M for inhibition of thrombin-induced 5-HT release from human platelets) with submicromolar binding affinity for the PAR-1 receptor (IC_{50} = 0.15 μ M). Compound fully inhibited thrombin-induced platelet aggregation but was inactive against ADP- or collagen-induced aggregation, and it did not inhibit thrombin catalytic activity (K_i > 10 μ M). Potentially useful for the treatment of thrombotic disorders.

SOURCE – Merck & Co.

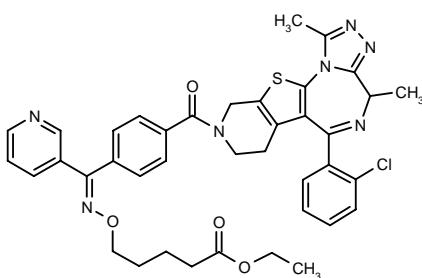
REFERENCES

1. Barrow, J.C. et al. (Merck & Co., Inc.) *Isoxazole thrombin receptor antagonists*. GB 2356198.

2. Nantermet, P.G. et al. *Discovery of a nonpeptide small molecule antagonist of the human platelet thrombin receptor (PAR-1)*. Bioorg Med Chem Lett 2002, 12(3): 319.

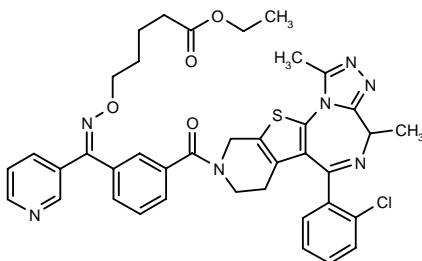
317372

5-[1-[4-[6-(2-Chlorophenyl)-1,4-dimethyl-7,8,9,10-tetrahydro-4*H*-pyrido[4',3':4,5]thieno[3,2-*f*][1,2,4]triazolo-[4,3-*a*][1,4]diazepin-9-ylcarbonylphenyl]-1-(3-pyridyl)-methylideneaminoxy]pentanoic acid ethyl ester



C39 H38 Cl N7 O4 S; Mol wt: 736.2932

ACTION – Antithrombotic agent, a dual-acting PAF receptor antagonist and thromboxane synthase inhibitor (IC_{50} = 0.10 and 0.072 μ M, respectively) proven able to protect mice from PAF-induced death (ED_{50} = 0.5 mg/kg p.o.) and to inhibit serum TxB_2 production *ex vivo* in rats. Another related compound is:



317371: C39 H38 Cl N7 O4 S

SOURCE – Nikken Chemicals.

REFERENCES

1. Fujita, M. et al. (Nikken Chemicals Co., Ltd.) *Triazolo-1,4-diazepine cpds. and medicinal compsn. containing the same*. EP 0995752, JP 1999071378, WO 9858930.

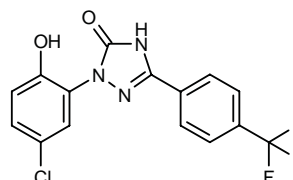
2. Fujita, M. et al. *Approach to dual-acting platelet activating factor (PAF) receptor antagonist/thromboxane synthase inhibitor (TxSI) based on the link of PAF antagonists and TxSIs*. Bioorg Med Chem Lett 2002, 12(3): 341.

RENAL-UROLOGIC DRUGS

TREATMENT OF URINARY INCONTINENCE

319253

2-(5-Chloro-2-hydroxyphenyl)-5-[4-(trifluoromethyl)-phenyl]-3,4-dihydro-2*H*-1,2,4-triazol-3-one



C15 H9 Cl F3 N3 O2; Mol wt: 355.7021

ACTION – Calcium-dependent, large-conductance potassium (maxi-K) channel opener proven to inhibit the contractile response induced by carbachol in rat bladder strips (87% at 20 μ M). Potentially useful for the treatment of urge urinary incontinence.

SOURCE – Bristol-Myers Squibb.

REFERENCES

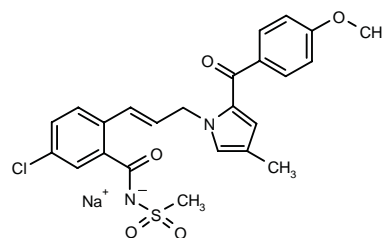
1. Romine, J.L. et al. (Bristol-Myers Squibb Co.) *Diphenyl oxadiazolones as potassium channel modulators*. JP 2000516925, US 5869509, WO 9804135.

2. Hewawasan, P. et al. *The synthesis and structure-activity relationships of 1,3-diaryl 1,2,4-(4*H*)-triazol-5-ones: A new class of calcium-dependent, large conductance, potassium (maxi-K) channel opener targeted for urge urinary incontinence*. Bioorg Med Chem Lett 2002, 12(7): 1117.

TREATMENT OF RENAL DISEASES

317288

5-Chloro-2-[3-[2-(4-methoxybenzoyl)-4-methyl-1*H*-pyrrol-1-yl]-1-propenyl]-*N*-(methylsulfonyl)benzamide sodium salt



C24 H22 Cl N2 Na O5 S; Mol wt: 508.9558

SOURCE – Merck & Co.

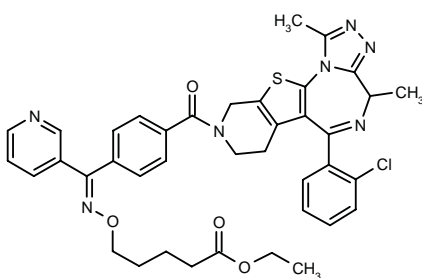
REFERENCES

1. Barrow, J.C. et al. (Merck & Co., Inc.) *Isoxazole thrombin receptor antagonists*. GB 2356198.

2. Nantermet, P.G. et al. *Discovery of a nonpeptide small molecule antagonist of the human platelet thrombin receptor (PAR-1)*. Bioorg Med Chem Lett 2002, 12(3): 319.

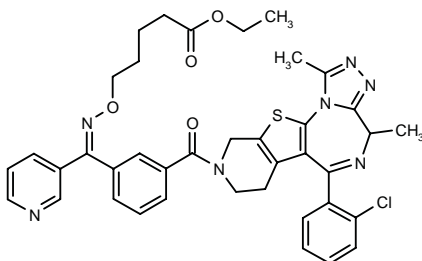
317372

5-[1-[4-[6-(2-Chlorophenyl)-1,4-dimethyl-7,8,9,10-tetrahydro-4*H*-pyrido[4',3':4,5]thieno[3,2-*f*][1,2,4]triazolo-[4,3-*a*][1,4]diazepin-9-ylcarbonylphenyl]-1-(3-pyridyl)-methylideneaminoxy]pentanoic acid ethyl ester



C₃₉ H₃₈ Cl N₇ O₄ S; Mol wt: 736.2932

ACTION – Antithrombotic agent, a dual-acting PAF receptor antagonist and thromboxane synthase inhibitor (IC₅₀ = 0.10 and 0.072 μM, respectively) proven able to protect mice from PAF-induced death (ED₅₀ = 0.5 mg/kg p.o.) and to inhibit serum TxB₂ production *ex vivo* in rats. Another related compound is:



317371: C₃₉ H₃₈ Cl N₇ O₄ S

SOURCE – Nikken Chemicals.

REFERENCES

1. Fujita, M. et al. (Nikken Chemicals Co., Ltd.) *Triazolo-1,4-diazepine cpds. and medicinal compsn. containing the same*. EP 0995752, JP 1999071378, WO 9858930.

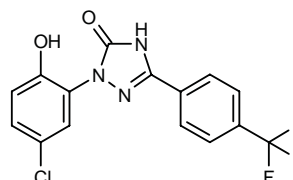
2. Fujita, M. et al. *Approach to dual-acting platelet activating factor (PAF) receptor antagonist/thromboxane synthase inhibitor (TxSI) based on the link of PAF antagonists and TxSIs*. Bioorg Med Chem Lett 2002, 12(3): 341.

RENAL-UROLOGIC DRUGS

TREATMENT OF URINARY INCONTINENCE

319253

2-(5-Chloro-2-hydroxyphenyl)-5-[4-(trifluoromethyl)-phenyl]-3,4-dihydro-2*H*-1,2,4-triazol-3-one



C₁₅ H₉ Cl F₃ N₃ O₂; Mol wt: 355.7021

ACTION – Calcium-dependent, large-conductance potassium (maxi-K) channel opener proven to inhibit the contractile response induced by carbachol in rat bladder strips (87% at 20 μM). Potentially useful for the treatment of urge urinary incontinence.

SOURCE – Bristol-Myers Squibb.

REFERENCES

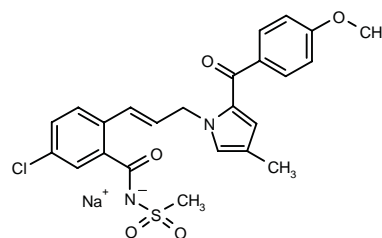
1. Romine, J.L. et al. (Bristol-Myers Squibb Co.) *Diphenyl oxadiazolones as potassium channel modulators*. JP 2000516925, US 5869509, WO 9804135.

2. Hewawasan, P. et al. *The synthesis and structure-activity relationships of 1,3-diaryl 1,2,4-(4*H*)-triazol-5-ones: A new class of calcium-dependent, large conductance, potassium (maxi-K) channel opener targeted for urge urinary incontinence*. Bioorg Med Chem Lett 2002, 12(7): 1117.

TREATMENT OF RENAL DISEASES

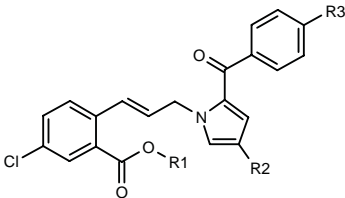
317288

5-Chloro-2-[3-[2-(4-methoxybenzoyl)-4-methyl-1*H*-pyrrol-1-yl]-1-propenyl]-*N*-(methylsulfonyl)benzamide sodium salt



C₂₄ H₂₂ Cl N₂ Na O₅ S; Mol wt: 508.9558

ACTION – TGF-β inhibitor, as demonstrated by its ability to suppress TGF-β-stimulated proteoglycan production in NRK-49F cells by 87% at 3 μM. In a rat model of nephritis induced by the anti-Thy-1 monoclonal antibody OX-7, oral administration of this compound (1.5-50 mg/kg/day for 7 days) dose-dependently reduced the kidney content of hydroxyproline, indicative of organ fibroid formation. Potentially useful for the treatment of a broad range of fibrotic disorders including nephropathy, glomerulonephritis, interstitial pneumonia, chronic obstructive pulmonary disease, asthma, hepatic cirrhosis, chronic pancreatitis, myocardial infarction, arteriosclerosis, restenosis after PTCA, bone marrow fibrosis, rheumatoid arthritis, atopic dermatitis, scleroderma, uterine myoma, prostatic hypertrophy, Alzheimer’s disease, sclerosing peritonitis, diabetic retinopathy, type 1 diabetes and postoperative organ adhesion. Other exemplified pyrrole derivatives are:



Compound	R1	R2	R3	Formula
317290	H	H	Me	C ₂₂ H ₁₆ ClNO ₃
317291	Na	Me	4-morpholinyl-CH ₂ CH ₂ O	C ₂₈ H ₂₆ ClN ₂ NaO ₅

SOURCE – Sumitomo Pharmaceuticals.

REFERENCES

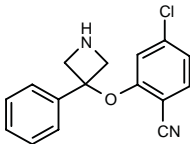
1. Tokunaga, T. et al. (Sumitomo Pharmaceuticals Co., Ltd.) *Pyrrole derivs.* WO 0210131.

GASTROINTESTINAL DRUGS

AGENTS FOR
INFLAMMATORY BOWEL DISEASE

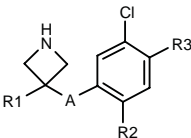
317231

4-Chloro-2-(3-phenylazetidin-3-yloxy)benzonitrile



C16 H13 Cl N2 O; Mol wt: 284.7447

ACTION – Agent with inducible nitric oxide synthase (iNOS)-inhibitory activity. This compound is considered to have potential in the treatment of inflammatory diseases, particularly inflammatory bowel disease, rheumatoid arthritis and osteoarthritis, and also in the treatment of pain. Other exemplified phenylheteroazetidines are:



Compound	R1	R2	R3	A	Formula
317232	2-thienyl	CN	H	O	C ₁₄ H ₁₁ ClN ₂ OS
317233	3-furyl	CN	F	O	C ₁₄ H ₁₀ ClFN ₂ O ₂
317234	2-furyl	CN	F	O	C ₁₄ H ₁₀ ClFN ₂ O ₂
317235	CF ₃	CN	F	O	C ₁₁ H ₇ ClF ₄ N ₂ O
317236	4-Me-2-thiazolyl	CN	F	O	C ₁₄ H ₁₁ ClFN ₃ OS
317237	2-thiazolyl	Cl	H	S	C ₁₂ H ₁₀ Cl ₂ N ₂ S ₂
317238	2-NH ₂ -4-thiazolyl	CN	F	O	C ₁₃ H ₁₀ ClFN ₄ OS
317239	Pr	CN	H	S	C ₁₃ H ₁₅ ClN ₂ S

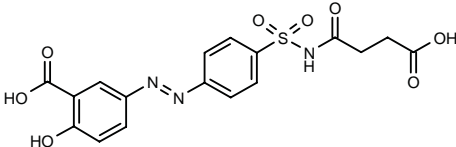
SOURCE – AstraZeneca.

REFERENCES

1. Cheshire, D. et al. (AstraZeneca AB) *Novel phenylheteroazetidines, useful as nitric oxide synthase inhibitors.* WO 0212187.

318255

2-Hydroxy-5-[4-[N-(4-hydroxysuccinyl)sulfamoyl]-phenylazo]benzoic acid



C17 H15 N3 O8 S; Mol wt: 421.3845

ACTION – A representative compound from a series of 5-aminosalicylic acid (5-ASA) derivatives for use as nonabsorbable antibiotics in the treatment of gastrointestinal disorders, especially Crohn’s disease, ulcerative colitis, traveler’s diarrhea and hepatic encephalopathy. The compound was shown to undergo azo reduction to yield 5-ASA when orally administered to rats.

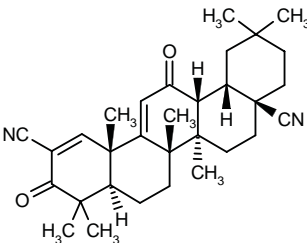
SOURCE – Nobex.

REFERENCES

1. Ekwuribe, N.N. et al. (Nobex Corp.) *5-ASA derivs. having anti-inflammatory and antibiotic activity and methods of treating diseases therewith.* WO 0218330.

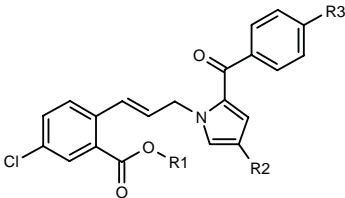
319214

2-Cyano-3,12-dioxooleanane-1,9(11)-diene-28-nitrile



C31 H40 N2 O2; Mol wt: 472.6690

ACTION – TGF-β inhibitor, as demonstrated by its ability to suppress TGF-β-stimulated proteoglycan production in NRK-49F cells by 87% at 3 μM. In a rat model of nephritis induced by the anti-Thy-1 monoclonal antibody OX-7, oral administration of this compound (1.5-50 mg/kg/day for 7 days) dose-dependently reduced the kidney content of hydroxyproline, indicative of organ fibroid formation. Potentially useful for the treatment of a broad range of fibrotic disorders including nephropathy, glomerulonephritis, interstitial pneumonia, chronic obstructive pulmonary disease, asthma, hepatic cirrhosis, chronic pancreatitis, myocardial infarction, arteriosclerosis, restenosis after PTCA, bone marrow fibrosis, rheumatoid arthritis, atopic dermatitis, scleroderma, uterine myoma, prostatic hypertrophy, Alzheimer’s disease, sclerosing peritonitis, diabetic retinopathy, type 1 diabetes and postoperative organ adhesion. Other exemplified pyrrole derivatives are:



Compound	R1	R2	R3	Formula
317290	H	H	Me	C ₂₂ H ₁₆ ClNO ₃
317291	Na	Me	4-morpholinyl-CH ₂ CH ₂ O	C ₂₈ H ₂₈ ClN ₂ NaO ₅

SOURCE – Sumitomo Pharmaceuticals.

REFERENCES

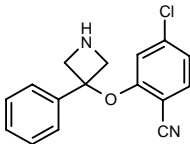
1. Tokunaga, T. et al. (Sumitomo Pharmaceuticals Co., Ltd.) *Pyrrole derivs.* WO 0210131.

GASTROINTESTINAL DRUGS

AGENTS FOR INFLAMMATORY BOWEL DISEASE

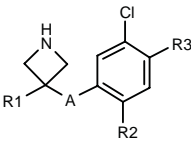
317231

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317234	2-furyl	CN	F	O	C ₁₄ H ₁₀ ClFN ₂ O ₂
317235	CF ₃	CN	F	O	C ₁₁ H ₇ ClF ₄ N ₂ O
317236	4-Me-2-thiazolyl	CN	F	O	C ₁₄ H ₁₁ ClFN ₃ OS
317237	2-thiazolyl	Cl	H	S	C ₁₂ H ₁₀ Cl ₂ N ₂ S ₂
317238	2-NH ₂ -4-thiazolyl	CN	F	O	C ₁₃ H ₁₀ ClFN ₄ OS
317239	Pr	CN	H	S	C ₁₃ H ₁₅ ClN ₂ S

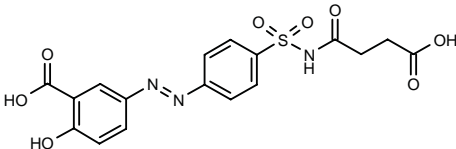
SOURCE – AstraZeneca.

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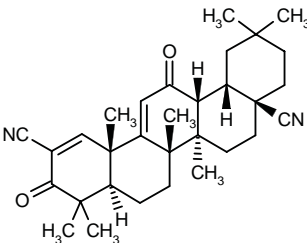
SOURCE – Nobex.

REFERENCES

1. Ekwuribe, N.N. et al. (Nobex Corp.) *5-ASA derivs. having anti-inflammatory and antibiotic activity and methods of treating diseases therewith.* WO 0218330.

319214

2-Cyano-3,12-dioxooleanane-1,9(11)-diene-28-nitrile



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ACTION – Synthetic triterpenoid able to inhibit nitric oxide (NO) production induced by interferon gamma in mouse macrophages with an IC₅₀ value approximately 30-fold lower than that of dexamethasone (IC₅₀ = 0.0035 and 0.10 nM, respectively) and good *in vivo* antiinflammatory activity after both oral and i.p. administration against peritoneal inflammation induced by thioglycollate and interferon gamma.

SOURCE – Dartmouth College, Hanover, NH (US).

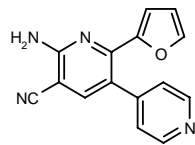
REFERENCES

1. Honda, T. et al. *A novel dicyanotriterpenoid, 2-cyano-3,12-dioxooleana-1,9(11)-dien-28-onitrile, active at picomolar concentrations for inhibition of nitric oxide production.* Bioorg Med Chem Lett 2002, 12(7): 1027.

TREATMENT OF DISORDERS OF GASTRIC EMPTYING

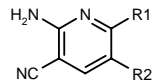
317892

6-Amino-2-(2-furyl)-3,4'-bipyridine-5-carbonitrile



C15 H10 N4 O; Mol wt: 262.2710

ACTION – Adenosine A₁, A_{2A} and A_{2B} antagonist (K_i = 990, 23 and 2.7 nM, respectively). *In vivo*, this compound was shown to dose-dependently increase defecation when orally administered to rats 3.5-, 14.5- and 44.5-fold, respectively, at doses of 1, 3 and 10 mg/kg. Potentially useful for the treatment of a broad range of adenosine-mediated disorders such as constipation, irritable bowel syndrome, inflammatory bowel disease, Crohn's disease, diabetes and complications related therewith, obesity, asthma, hypertension, osteoporosis, Parkinson's disease and Alzheimer's disease. Other exemplified 2-amino-pyridine compounds include the following:



Compound	R1	R2	Formula
317893	3-F-Ph	4-Pyr	C ₁₇ H ₁₁ N ₄
317894	2-furyl	1-Et-6-oxo-1,6-dihydro-3-Pyr	C ₁₇ H ₁₄ N ₄ O ₂

SOURCE – Eisai.

REFERENCES

1. Harada, H. et al. (Eisai Co., Ltd.) *2-Aminopyridine cpds. and use thereof as drugs.* WO 0214282.

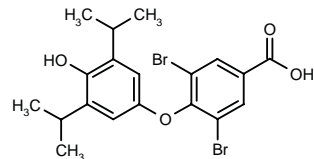
ENDOCRINE DRUGS

THYROID DISEASE THERAPY

DIBRT

318801

3,5-Dibromo-4-(4-hydroxy-3,5-diisopropylphenoxy)-benzoic acid



C19 H20 Br2 O4; Mol wt: 472.1710

ACTION – Thyroid hormone receptor (TR) antagonist able to block TR binding of T₃ (K_d = 1380 nM), as well as the ability of T₃ to stimulate coactivator binding. Compound showed no agonist activity at TR α and weak partial agonist activity at TR β . Potentially useful for the treatment of hyperthyroidism, arrhythmias, heart failure, weakness and nervousness.

SOURCES – University of California, San Francisco, CA (US); Karo Bio.

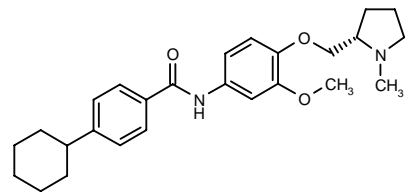
REFERENCES

1. Scanlan, T.S. et al. (University of California, Oakland) *Nuclear receptor ligands and ligand binding domains.* WO 9721993.
2. Scanlan, T.S. et al. (University of California, Oakland) *Nuclear receptor ligands and ligand binding domains.* WO 9926966.
3. Baxter, J.D. et al. *Structure-based design and synthesis of a thyroid hormone receptor (TR) antagonist.* Endocrinology 2002, 143(2): 517.

ANTIDIABETIC DRUGS

316914

4-Cyclohexyl-N-[3-methoxy-4-[1-methylpyrrolidin-2(S)-ylmethoxy]phenyl]benzamide



C26 H34 N2 O3; Mol wt: 422.5656

ACTION – Synthetic triterpenoid able to inhibit nitric oxide (NO) production induced by interferon gamma in mouse macrophages with an IC₅₀ value approximately 30-fold lower than that of dexamethasone (IC₅₀ = 0.0035 and 0.10 nM, respectively) and good *in vivo* antiinflammatory activity after both oral and i.p. administration against peritoneal inflammation induced by thioglycollate and interferon gamma.

SOURCE – Dartmouth College, Hanover, NH (US).

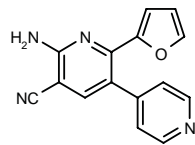
REFERENCES

1. Honda, T. et al. *A novel dicyanotriterpenoid, 2-cyano-3,12-dioxooleana-1,9(11)-dien-28-onitrile, active at picomolar concentrations for inhibition of nitric oxide production.* Bioorg Med Chem Lett 2002, 12(7): 1027.

TREATMENT OF DISORDERS OF GASTRIC EMPTYING

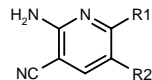
317892

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ACTION – Adenosine A₁, A_{2A} and A_{2B} antagonist (K_i = 990, 23 and 2.7 nM, respectively). *In vivo*, this compound was shown to dose-dependently increase defecation when orally administered to rats 3.5-, 14.5- and 44.5-fold, respectively, at doses of 1, 3 and 10 mg/kg. Potentially useful for the treatment of a broad range of adenosine-mediated disorders such as constipation, irritable bowel syndrome, inflammatory bowel disease, Crohn's disease, diabetes and complications related therewith, obesity, asthma, hypertension, osteoporosis, Parkinson's disease and Alzheimer's disease. Other exemplified 2-amino-pyridine compounds include the following:



Compound	R1	R2	Formula
317893	3-F-Ph	4-Pyr	C ₁₇ H ₁₁ N ₄
317894	2-furyl	1-Et-6-oxo-1,6-dihydro-3-Pyr	C ₁₇ H ₁₄ N ₄ O ₂

SOURCE – Eisai.

REFERENCES

1. Harada, H. et al. (Eisai Co., Ltd.) *2-Aminopyridine cpds. and use thereof as drugs.* WO 0214282.

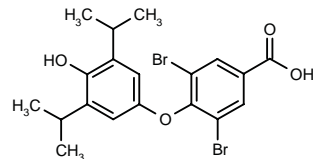
ENDOCRINE DRUGS

THYROID DISEASE THERAPY

DIBRT

318801

3,5-Dibromo-4-(4-hydroxy-3,5-diisopropylphenoxy)-benzoic acid



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ACTION – Thyroid hormone receptor (TR) antagonist able to block TR binding of T₃ (K_d = 1380 nM), as well as the ability of T₃ to stimulate coactivator binding. Compound showed no agonist activity at TR α and weak partial agonist activity at TR β . Potentially useful for the treatment of hyperthyroidism, arrhythmias, heart failure, weakness and nervousness.

SOURCES – University of California, San Francisco, CA (US); Karo Bio.

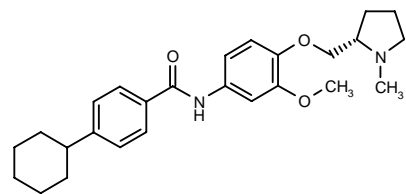
REFERENCES

1. Scanlan, T.S. et al. (University of California, Oakland) *Nuclear receptor ligands and ligand binding domains.* WO 9721993.
2. Scanlan, T.S. et al. (University of California, Oakland) *Nuclear receptor ligands and ligand binding domains.* WO 9926966.
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ANTIDIABETIC DRUGS

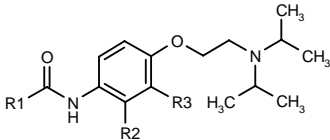
316914

4-Cyclohexyl-N-[3-methoxy-4-[1-methylpyrrolidin-2(S)-ylmethoxy]phenyl]benzamide

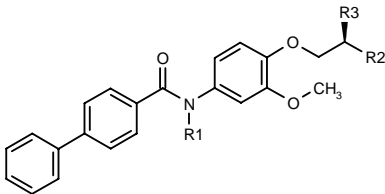


C26 H34 N2 O3; Mol wt: 422.5656

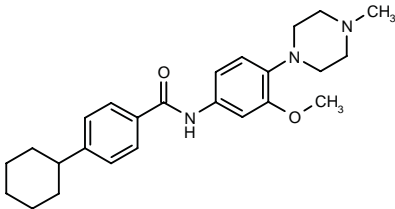
ACTION – An antagonist of the human 11CBy receptor giving a pK_i of 7.5-7.8 in radioligand binding studies using HEK293 membranes expressing 11CBy receptors. Potentially useful for the treatment of diabetes, depression, anxiety, schizophrenia and sleep disorders. Other exemplified carboxamide compounds are:



Compound	R1	R2	R3	Formula
316915	4-(PhCH2)-Ph	H	OMe	C ₂₉ H ₃₆ N ₂ O ₃
316916	2-Cl-4-Ph-Ph	H	OMe	C ₂₈ H ₃₃ ClN ₂ O ₃
316917	4-cyclohexyl-Ph	F	H	C ₂₇ H ₃₇ FN ₂ O ₂
316919	6-Ph-3-Pyr	H	OMe	C ₂₇ H ₃₃ N ₃ O ₃



Compound	R1	R2	R3	Formula
316918	Me	N(Et)2	H	C ₂₇ H ₃₂ N ₂ O ₃
316920	H	CH2N(Et)2	OH	C ₂₇ H ₃₂ N ₂ O ₄



316921: C₂₅ H₃₃ N₃ O₂

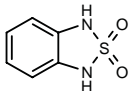
SOURCE – GlaxoSmithKline.

REFERENCES

1. Johnson, C.N. et al. (GlaxoSmithKline plc) *Carboxamide cpds. and their use as antagonists of a human 11CBy receptor*. WO 0210146.

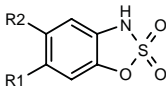
317051

1,3-Dihydro-2,1,3-benzothiadiazole 2,2-dioxide

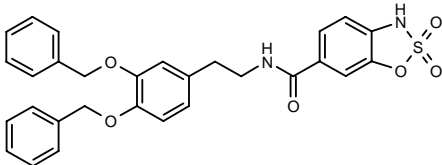


C₆ H₆ N₂ O₂ S; Mol wt: 170.1914

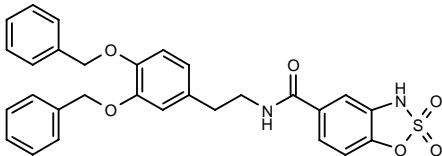
ACTION – An inhibitor of protein phosphatases, particularly PTP1B, CD45, LAR, SHP-1, SHP-2, PTPa and HePTP, expected to be useful for the treatment of type 1 diabetes, type 2 diabetes, obesity and insulin resistance. Other exemplified compounds are:



Compound	R1	R2	Formula
317052	Me	H	C ₇ H ₇ NO ₃ S
317053	H	Me	C ₇ H ₇ NO ₃ S
317055	NO ₂	H	C ₆ H ₄ N ₂ O ₅ S
317056	H	CO ₂ Me	C ₈ H ₇ NO ₅ S
317058	H	CONHC16H33	C ₂₃ H ₃₈ N ₂ O ₄ S
317059	CO ₂ H	H	C ₇ H ₅ NO ₅ S



317062: C₂₉ H₂₆ N₂ O₆ S



317057: C₂₉ H₂₆ N₂ O₆ S

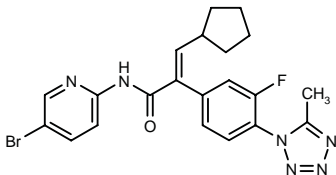
SOURCE – Aventis Pharma.

REFERENCES

1. Petry, S. et al. (Aventis Pharma Deutschland GmbH) *Substd. and non-substd. benzooxathiazoles and cpds. derived therefrom*. DE 10038709, WO 0211722.

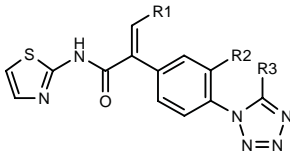
317533

N-(5-Bromopyridin-2-yl)-3-cyclopentyl-2-[3-fluoro-4-(5-methyl-1H-tetrazol-1-yl)phenyl]-2(E)-propenamide

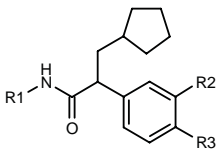


C₂₁ H₂₀ Br F N₆ O; Mol wt: 471.3320

ACTION – Glucokinase activator, potentially useful for the prevention and treatment of type 2 diabetes. Other specifically claimed tetrazole-containing 2-phenyl-acetamide derivatives are:



Compound	R1	R2	R3	Formula
317534	cyclopentyl	Cl	Me	C ₁₉ H ₁₉ ClN ₆ OS
317535	cyclohexyl	Cl	CF ₃	C ₂₀ H ₁₈ ClF ₃ N ₆ OS
317540	cyclohexyl	Cl	Me	C ₂₀ H ₂₁ ClN ₆ OS
317541	cyclopentyl	F	Me	C ₁₉ H ₁₉ FN ₆ OS



Compound	R1	R2	R3	Formula
317536	5-Br-2-Pyr	F	5-Me-1-tetrazolyl	C ₂₁ H ₂₂ BrFN ₆ O
317537	2-thiazolyl	Cl	5-Me-1-tetrazolyl	C ₁₉ H ₂₁ ClN ₆ OS
317538	2-thiazolyl	5-Me-1-tetrazolyl	SO ₂ Me	C ₂₀ H ₂₄ N ₆ O ₃ S ₂
317539	5-Br-2-Pyr	Cl	5-Me-1-tetrazolyl	C ₂₁ H ₂₂ BrClN ₆ O

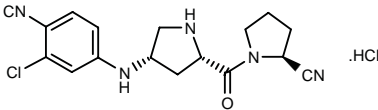
SOURCE – Roche.

REFERENCES

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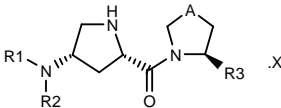
317819

1-[4(S)-(3-Chloro-4-cyanophenylamino)pyrrolidin-2(S)-ylcarbonyl]pyrrolidine-2(S)-carbonitrile hydrochloride

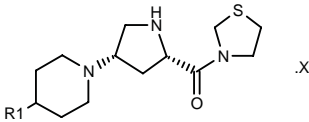


C17 H18 Cl N5 O . HCl; Mol wt: 380.2771

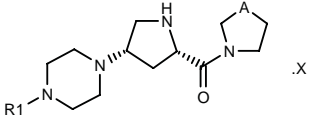
ACTION – A dipeptidyl-peptidase IV (DPP-IV) inhibitor (IC₅₀ = 0.13 and 0.15 nM in human and rat plasma, respectively), potentially useful for the treatment of diabetes, obesity, HIV infection, cancer, dermatopathy, prostatic hypertrophy, periodontal disease and autoimmune diseases. Other exemplified proline derivatives include the following:



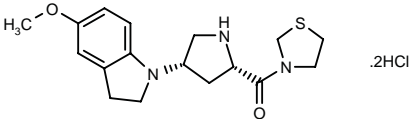
Compound	R1	R2	R3	A	X	Formula
317820	H	4-NO ₂ -Ph	CN	CH ₂	HCl	C ₁₆ H ₁₉ N ₅ O ₃ .HCl
317821	H	5-CF ₃ -2-Pyr	CN	CH ₂	2CF ₃ CO ₂ H	C ₁₆ H ₁₈ F ₃ N ₅ O.2C ₂ HF ₃ O ₂
317822	H	2-pyrimidinyl	CN	CH ₂	HCl	C ₁₄ H ₁₈ N ₆ O.HCl
317823	H	4-NO ₂ -PhCH ₂	CN	CH ₂	2HCl	C ₁₇ H ₂₁ N ₅ O ₃ .2HCl
317824	CH ₂ CO ₂ Et	CH ₂ CO ₂ Et	CN	CH ₂	2HCl	C ₁₈ H ₂₈ N ₄ O ₅ .2HCl
317826	Me	3-CN-PhCH ₂	H	S	2HCl	C ₁₇ H ₂₂ N ₄ OS.2HCl



Compound	R1	X	Formula
317829	2-benzothieryl	2HCl	C ₂₁ H ₂₇ N ₃ OS ₂ .2HCl
317837	4-(4-morpholinyl-CH ₂ CH ₂)-5-oxo-4H-1,3,4-oxadiazol-2-yl	3HCl	C ₂₁ H ₃₄ N ₆ O ₄ S.3HCl
317838	5-F-2-benzimidazolyl	3HCl	C ₂₀ H ₂₆ FN ₅ OS.3HCl



Compound	R1	A	X	Formula
317831	5-NO ₂ -2-Pyr	CH ₂	3HCl	C ₁₈ H ₂₆ N ₆ O ₃ .3HCl
317832	4-quinolyl	S	3HCl	C ₂₁ H ₂₇ N ₅ OS.3HCl
317833	5-CO ₂ H-2-Pyr	S	3HCl	C ₁₈ H ₂₈ N ₅ O ₃ .3HCl
317834	6-CF ₃ -2-benzothiazolyl	S	2HCl	C ₂₀ H ₂₄ F ₃ N ₅ OS ₂ .2HCl
317836	4-Cl-1-isoquinolyl	S	3HCl	C ₂₁ H ₂₆ ClN ₅ OS.3HCl



317825: C17 H23 N3 O2 S . 2HCl

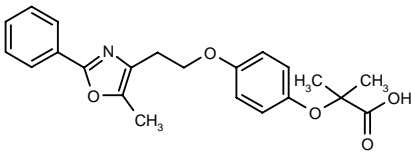
SOURCE – Mitsubishi Pharma.

REFERENCES

1. Kitajima, H. et al. (Welfide Corp.) *Proline derivs. and use thereof as drugs*. WO 0214271.

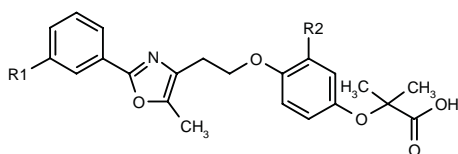
318264

2-Methyl-2-[4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]-phenoxy]propionic acid



C22 H23 N O5; Mol wt: 381.4257

ACTION – Peroxisome proliferator-activated receptor (PPAR) inhibitor that was shown to bind to PPAR α and PPAR γ with IC₅₀ values of 1677 and 2127 nM, respectively. When orally administered to HuapoAl transgenic mice (30 mg/kg/day for 7 days), it produced a 79.2% reduction in serum triglycerides and a 77% increase in HDL cholesterol levels. In diabetic mice, oral administration following the same schedule resulted in a 38% glucose normalization rate. Potentially useful for the prevention and treatment of diabetes, cardiovascular diseases and syndrome X. Other exemplified oxazole-containing carboxylic acids include the following:



Compound	R1	R2	Formula
318265	Br	H	C ₂₂ H ₂₂ BrNO ₅
318266	H	Et	C ₂₄ H ₂₇ NO ₅

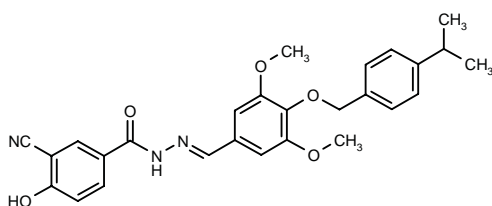
SOURCE – Lilly.

REFERENCES

1. Brooks, D.A. et al. (Eli Lilly and Company) *Oxazolyl-aryloxyacetic acid derivs. and their use as PPAR agonists*. WO 0218355.

318604

3-Cyano-4-hydroxy-*N*'-[4-(4-isopropylbenzyloxy)-3,5-dimethoxybenzylidene]benzohydrazide



C₂₇ H₂₇ N₃ O₅: Mol wt: 473.5263

ACTION – Glucagon receptor antagonist ($IC_{50} = 20$ and 1.0 nM for binding affinity at human and rat receptor, respectively) shown to significantly reduce glucose levels in fasted rats at 3 mg/kg i.v. without affecting glucose levels in fed rats. Potentially useful for the treatment of diabetes.

SOURCES – Agouron (Pfizer); Novo Nordisk.

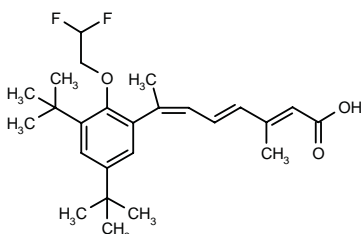
REFERENCES

1. Gonzales, J. et al. (Novo Nordisk A/S; Alanex Corp.) *Glucagon antagonists/inverse agonists*. EP 0994848, WO 9901423.
2. Ling, A. et al. *Human glucagon receptor antagonists based on alkylidene hydrazides*. Bioorg Med Chem Lett 2002. 12(4): 663.

LG-101506

317874

7-[3,5-Di-*tert*-butyl-2-(2,2-difluoroethoxy)phenyl]-3-methyl-2(*E*).4(*E*).6(*Z*)-octatrienoic acid



C25 H34 F2 O3; Mol wt: 420.5366

ACTION – Retinoid X receptor (RXR) modulator proven to lower plasma glucose in insulin-resistant *db/db* mice and to increase HDL cholesterol in human apolipoprotein A-I transgenic mice. Potentially useful for the treatment of type 2 diabetes.

SOURCE – Ligand.

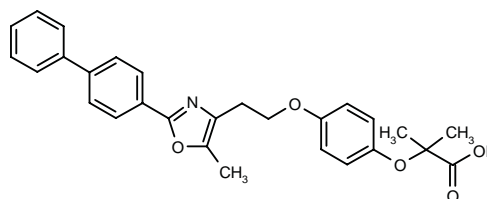
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1. Ardecky, R.J. et al. (Ligand Pharmaceuticals, Inc.) *RXR modulators with improved pharmacologic profile*. WO 0119770.
2. Michellys, P.-Y. et al. *RXR modulators. New small molecules for the treatment of type II diabetes?* 223rd ACS Natl Meet (April 7-11, Orlando) 2002, Abst MEDI 5.

LY-465608*

302324

2-[4-[2-[2-(Biphenyl-4-yl)-5-methyloxazol-4-yl]ethoxy]-phenoxy]-2-methylpropionic acid

C₂₈ H₂₇ N O₅; Mol wt: 457.5233

ACTION – Nonthiazolidinedione dual peroxisome proliferator-activated receptor PPAR α /PPAR γ agonist with high affinity for human PPAR α and PPAR γ receptors (IC₅₀ = 174 and 548 nM, respectively) and poor affinity (K_d > 10 μ M) for a panel of other receptors including retinoic acid receptors, retinoid X receptors, glucocorticoid receptors and thyroid receptors. In cotransfection assays, compound demonstrated full agonist activity at human PPAR α and PPAR γ receptors (EC₅₀ = 149 and 882 nM, respectively), as well as at mouse PPAR α receptors (EC₅₀ = 2.56 μ M). In hyperglycemic male Zucker diabetic fatty (ZDF) rats, it dose-dependently reduced plasma glucose levels (ED₅₀ = 3.8 mg/kg/day p.o.), and it significantly enhanced insulin sensitivity in female obese Zucker rats at 10 and 30 mg/kg/day. It also produced a dose-dependent elevation in HDL cholesterol and reduction in plasma triglyceride levels in human apolipoprotein A-I transgenic mice, with respective changes of +154% and -90% at the dose of 30 mg/kg/day. Long-term administration (28 days) of compound to ZDF rats was associated with favorable metabolic changes, with no increase in food consumption and poor body weight gain. Potentially useful for the treatment of type 2 diabetes.

SOURCES – Ligand; Lilly.

REFERENCES

1. Brooks, D.A. et al. (Eli Lilly and Company; Ligand Pharmaceuticals, Inc.) *Biaryl-oxa(thia)zole derivs. and their use as PPARs modulators*. WO 0116120.
2. Brooks, D.A. et al. *Design and synthesis of 2-methyl-2-[4-[2-(5-methyl-2-aryloxazol-4-yl)ethoxy]phenyl]propionic acids: A new class of dual PPAR α/γ agonists*. J Med Chem 2001, 44(13): 2061.

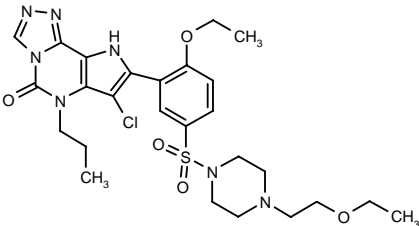
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*Identified compound **302324** (see **302323**) Drug Data Rep 2001, 023(08): 0782.

TREATMENT OF MALE SEXUAL DYSFUNCTION

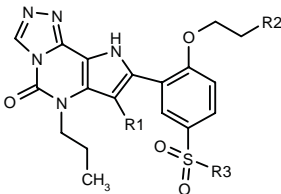
317093

7-Chloro-8-[2-ethoxy-5-[4-(2-ethoxyethyl)piperazin-1-ylsulfonyl]phenyl]-6-propyl-6,9-dihydro-5*H*-pyrrolo[2,3-*e*]-[1,2,4]triazolo[4,3-*c*]pyrimidin-5-one



C26 H34 Cl N7 O5 S; Mol wt: 592.1176

ACTION – Phosphodiesterase type 5 (PDE5) inhibitor with an IC₅₀ of 0.0142 nM against PDE5 from human platelet lysates. Potentially useful for the treatment of angina, hypertension, pulmonary hypertension, congestive heart failure, renal failure, atherosclerosis, conditions of reduced blood vessel patency, peripheral vascular disease, stroke, bronchitis, asthma, allergic rhinitis, glaucoma, male erectile dysfunction, female sexual dysfunction and diseases associated with disorders of gut motility. Other exemplified pyrrolotriazolopyrimidinones are:



Compound	R1	R2	R3	Formula
317094	Cl	H	4-Me-perhydro-1,4-diazepin-1-yl	C ₂₄ H ₃₀ ClN ₇ O ₅ S
317095	Cl	Me	4-[(CH ₂) ₃ OH]-1-Piz	C ₂₆ H ₃₄ ClN ₇ O ₅ S
317096	Cl	Me	2,2,6,6-(Me) ₄ -4-Pip-NH	C ₂₈ H ₃₈ ClN ₇ O ₅ S
317097	Cl	Me	4-allyl-1-Piz	C ₂₆ H ₃₂ ClN ₇ O ₅ S
317098	Cl	Me	NHCH ₂ CH ₂ OH	C ₂₁ H ₂₅ ClN ₆ O ₅ S
317099	Br	Me	4-Me-1-Piz	C ₂₄ H ₃₀ BrN ₇ O ₅ S
317100	Br	Me	4-(CH ₂ CH ₂ OH)-perhydro-1,4-diazepin-1-yl	C ₂₆ H ₃₄ BrN ₇ O ₅ S
317101	Br	Me	4-(CH ₂ CH ₂ OH)-1-Piz	C ₂₅ H ₃₂ BrN ₇ O ₅ S
317102	Br	Me	1-Piz	C ₂₃ H ₂₈ BrN ₇ O ₅ S
317103	Cl	H	8a(S)-perhydro-pyrrolo-[1,2-a]pyrazin-2-yl	C ₂₅ H ₃₀ ClN ₇ O ₅ S
317104	Cl	H	(1 <i>S</i> ,4 <i>S</i>)-5-Me-2,5-diazabicyclo[2.2.1]hept-1-yl	C ₂₄ H ₂₈ ClN ₇ O ₅ S

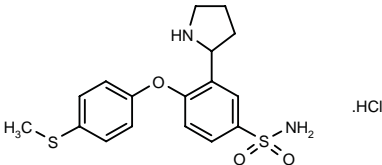
SOURCE – Almirall Prodesfarma.

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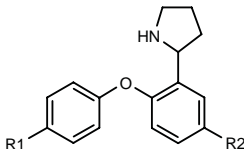
318032

(+)-4-[4-(Methylsulfonyl)phenoxy]-3-(2-pyrrolidiny)-benzenesulfonamide hydrochloride



C17 H20 N2 O3 S2 . HCl; Mol wt: 400.9489

ACTION – Selective 5-HT reuptake inhibitor (IC₅₀ = 5.4 nM) with potential in the treatment of premature ejaculation, as well as other 5-HT-mediated disorders including depression, attention deficit hyperactivity disorder, obsessive-compulsive disorder, posttraumatic stress disorder, drug abuse and sexual dysfunction. Other specifically claimed phenoxyphenylheterocycle derivatives are:



Compound	R1	R2	Formula
318033	SMe	SO ₂ NHMe	C ₁₈ H ₂₂ N ₂ O ₃ S ₂
318034	OCF ₃	N(Me)SO ₂ Me	C ₁₉ H ₂₁ F ₃ N ₂ O ₄ S
318035	OCF ₃	NHSO ₂ Me	C ₁₈ H ₁₉ F ₃ N ₂ O ₄ S

SOURCE – Pfizer.

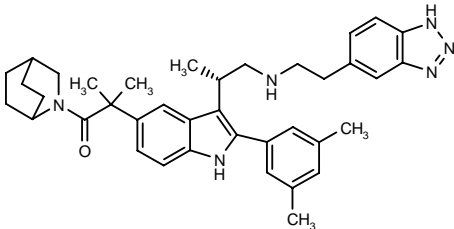
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1. Andrews, M.D. et al. (Pfizer Ltd.;Pfizer Inc.) *Phenoxyphenylheterocycle derivs. as selective serotonin reuptake inhibitors (SSRIs).* EP 1184372.

TREATMENT OF GYNECOLOGICAL DISORDERS

317328

N-[2(*S*)-[5-[2-(2-Azabicyclo[2.2.2]oct-2-yl)-1,1-dimethyl-2-oxoethyl]-2-(3,5-dimethylphenyl)-1*H*-indol-3-yl]propyl]-*N*-[2-(1*H*-1,2,3-benzotriazol-5-yl)ethyl]amine



C38 H46 N6 O; Mol wt: 602.8224

ACTION – Gonadotropin-releasing hormone (GnRH) antagonist (IC_{50} = 2.5 nM for inhibition of GnRH-stimulated inositol phosphate hydrolysis) with subnanomolar affinity for the GnRH receptor (IC_{50} = 0.3 nM). In castrated rats, oral doses of 1-20 mg/kg inhibited the release of luteinizing hormone (LH) and a substantial reduction in plasma LH levels was seen at the highest doses for 14 h. Potentially useful for the treatment of gynecological disorders.

SOURCE – Merck & Co.

REFERENCES

1. Goulet, M. et al. (Merck & Co., Inc.) *Antagonists of gonadotropin releasing hormone*. EP 1095038, WO 0004013.

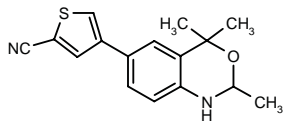
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3. Young, J.R. et al. *2-Arylindoles as gonadotropin releasing hormone (GnRH) antagonists: Optimization of the tryptamine side chain*. Bioorg Med Chem Lett 2002, 12(5): 827.

CONTRACEPTIVES

317310

4-(2,4,4-Trimethyl-1,4-dihydro-2H-3,1-benzoxazin-6-yl)-thiophene-2-carbonitrile



C16 H16 N2 O S; Mol wt: 284.3814

ACTION – Potent nonsteroidal progesterone receptor agonist with an EC_{50} value of 0.35 nM in the alkaline phosphate assay and high binding affinity for the progesterone receptor (IC_{50} = 11.5 nM). *In vivo*, compound was more potent than progesterone in the decidualization assay in ovariectomized female rats after s.c. administration (ED_{50} = 1.50 and 5.62 mg/kg, respectively). Potentially useful as a female contraceptive and for hormone replacement therapy in combination with estrogen.

SOURCES – Ligand; Wyeth.

REFERENCES

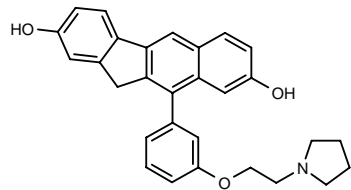
1. Grubb, G.S. et al. (American Home Products Corp.;Ligand Pharmaceuticals, Inc.) *Contraceptive compsns. containing quinazolinone and benzoxazine derivs..* WO 0066164, WO 0066165.

2. Zhang, P. et al. (American Home Products Corp.;Ligand Pharmaceuticals, Inc.) *Quinazolinone and benzoxazine derivs. as progesterone receptor modulators*. EP 1175404, WO 0066560.

3. Zhang, P. et al. *Potent nonsteroidal progesterone receptor agonists: Synthesis and SAR study of 6-aryl benzoxazines*. Bioorg Med Chem Lett 2002, 12(5): 787.

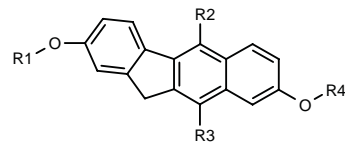
318065

10-[3-[2-(1-Pyrrolidinyl)ethoxy]phenyl]-11H-benzo[b]-fluorene-2,8-diol



C29 H27 N O3; Mol wt: 437.5363

ACTION – Estrogen receptor (ER) modulator that demonstrated ER β receptor-antagonist activity *in vitro* in human ER β -transfected CHO cells. For use in contraception, benign prostatic hypertrophy, cardiovascular disorders, menopausal complaints, osteoporosis, estrogen-dependent tumors, depression and Alzheimer's disease. Other exemplified 10-aryl-11H-benzo[b]fluorene derivatives are:



Compound	R1	R2	R3	R4	Formula
318067	H	H	3-[N(Me)2CH2CH2O]-Ph	H	C27H25NO3
318069	H	H	3-(4-morpholinyl-CH2CH2O)-Ph	H	C29H27NO4
318071	H	H	3-[N(Et)2CH2CH2O]-Ph	H	C29H29NO3
318073	H	H	3-(1-Pip-CH2CH2O)-Ph	H	C30H29NO3
318074	H	H	3-[1-Pip-(CH2)4O]-Ph	H	C32H33NO3
318075	Me	Cl	OH	Me	C19H15ClO3

SOURCE – Akzo Nobel.

REFERENCES

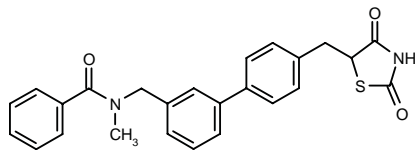
1. Veeneman, G.H. et al. (Akzo Nobel N.V.) *10-Aryl-11H-benzo[b]fluorene derivs. and analogs for medicinal use*. WO 0216316.

DERMATOLOGIC DRUGS

ACNE THERAPY

317176

N-[4'-(2,4-Dioxothiazolidin-5-ylmethyl)biphenyl-3-ylmethyl]-N-methylbenzamide



C25 H22 N2 O3 S; Mol wt: 430.5258

ACTION – Gonadotropin-releasing hormone (GnRH) antagonist (IC_{50} = 2.5 nM for inhibition of GnRH-stimulated inositol phosphate hydrolysis) with subnanomolar affinity for the GnRH receptor (IC_{50} = 0.3 nM). In castrated rats, oral doses of 1-20 mg/kg inhibited the release of luteinizing hormone (LH) and a substantial reduction in plasma LH levels was seen at the highest doses for 14 h. Potentially useful for the treatment of gynecological disorders.

SOURCE – Merck & Co.

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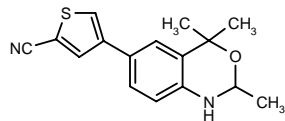
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CONTRACEPTIVES

317310

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C16 H16 N2 O S; Mol wt: 284.3814

ACTION – Potent nonsteroidal progesterone receptor agonist with an EC_{50} value of 0.35 nM in the alkaline phosphate assay and high binding affinity for the progesterone receptor (IC_{50} = 11.5 nM). *In vivo*, compound was more potent than progesterone in the decidualization assay in ovariectomized female rats after s.c. administration (ED_{50} = 1.50 and 5.62 mg/kg, respectively). Potentially useful as a female contraceptive and for hormone replacement therapy in combination with estrogen.

SOURCES – Ligand; Wyeth.

REFERENCES

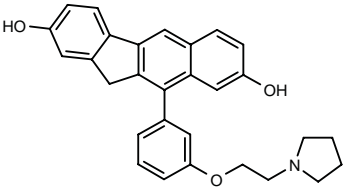
1. Grubb, G.S. et al. (American Home Products Corp.;Ligand Pharmaceuticals, Inc.) *Contraceptive compsns. containing quinazolinone and benzoxazine derivs..* WO 0066164, WO 0066165.

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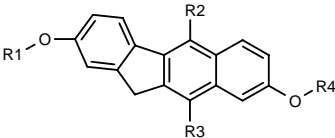
318065

10-[3-[2-(1-Pyrrolidinyl)ethoxy]phenyl]-11H-benzo[b]-fluorene-2,8-diol



C29 H27 N O3; Mol wt: 437.5363

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Compound	R1	R2	R3	R4	Formula
318067	H	H	3-[N(Me)2CH2CH2O]-Ph	H	C27H25NO3
318069	H	H	3-(4-morpholinyl-CH2CH2O)-Ph	H	C29H27NO4
318071	H	H	3-[N(Et)2CH2CH2O]-Ph	H	C29H29NO3
318073	H	H	3-(1-Pip-CH2CH2O)-Ph	H	C30H29NO3
318074	H	H	3-[1-Pip-(CH2)4O]-Ph	H	C32H33NO3
318075	Me	Cl	OH	Me	C19H15ClO3

SOURCE – Akzo Nobel.

REFERENCES

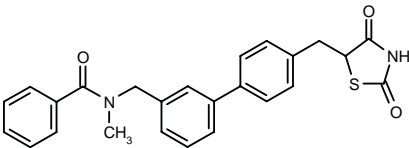
1. Veeneman, G.H. et al. (Akzo Nobel N.V.) *10-Aryl-11H-benzo[b]fluorene derivs. and analogs for medicinal use*. WO 0216316.

DERMATOLOGIC DRUGS

ACNE THERAPY

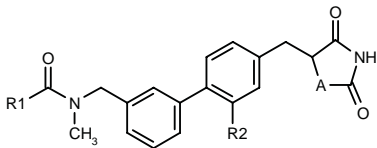
317176

N-[4'-(2,4-Dioxothiazolidin-5-ylmethyl)biphenyl-3-ylmethyl]-N-methylbenzamide

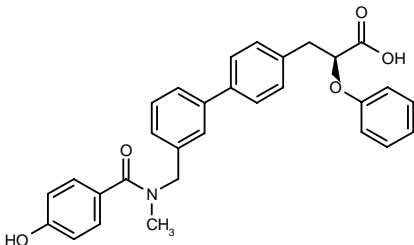


C25 H22 N2 O3 S; Mol wt: 430.5258

ACTION – Peroxisome proliferator-activated receptor PPAR γ agonist, potentially useful for the treatment of dermatological keratinization disorders including acne, ichthyosis, psoriasis, atopic dermatitis, eczema, gingival hypertrophy, papillomatoses, T-cell lymphoma, dermatoses and pigmentation disorders. Other specifically claimed biphenyl derivatives include the following:



Compound	R1	R2	A	Formula
317177	C8H17	H	S	C ₂₇ H ₃₄ N ₂ O ₃ S
317178	C7H15	H	S	C ₂₆ H ₃₂ N ₂ O ₃ S
317179	4-F-Ph	H	S	C ₂₅ H ₂₁ FN ₂ O ₃ S
317180	4-AcO-Ph	H	S	C ₂₇ H ₂₄ N ₂ O ₅ S
317182	C6H13	H	CH2	C ₂₆ H ₃₂ N ₂ O ₃
317183	C7H15	Me	S	C ₂₇ H ₃₄ N ₂ O ₃ S
317184	4-BuO-PhNH	H	S	C ₂₉ H ₃₁ N ₃ O ₄ S



317185: C30 H27 N O5

SOURCE – Galderma.

REFERENCES

1. Bernardon, J.-M. and Clary, L. (Laboratoires Galderma SA) *Biphenyl derivs. and their use as PPAR- γ receptor activators.* FR 2812876, WO 0212210.

ANTIPSORIATICS

MAb C340

317230

Monoclonal antibody to human interleukin-12

C340

ACTION – Anti-human interleukin-12 (IL-12) antibody found to inhibit interferon gamma production stimulated with IL-2 plus IL-12 in peripheral blood mononuclear cells. It also inhibited IL-12 plus IL-2-induced LAK cell cytotoxicity. Potentially useful for the treatment of psoriasis and multiple sclerosis.

SOURCE – Centocor.

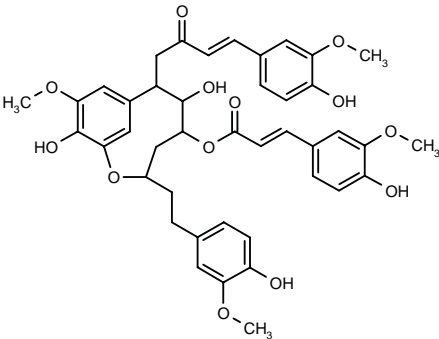
REFERENCES

1. Giles-Komar, J. et al. (Centocor Inc.) *Anti-IL-12 antibodies, compsns., methods and uses.* WO 0212500.

MISCELLANEOUS
DERMATOLOGIC DRUGS

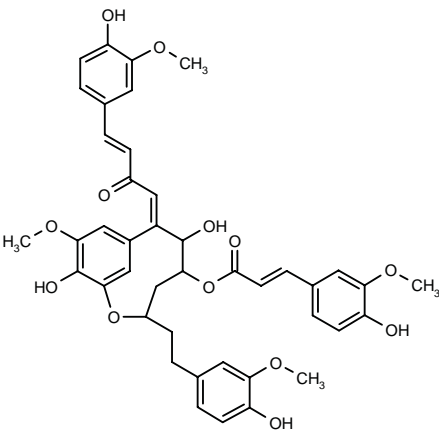
317013

3-(4-Hydroxy-3-methoxyphenyl)-2-propenoic acid 6,11-dihydroxy-3-[2-(4-hydroxy-3-methoxyphenyl)ethyl]-7-[4-(4-hydroxy-3-methoxyphenyl)-2-oxo-3-butenyl]-10-methoxy-2-oxabicyclo[6.3.1]dodeca-1(12),8,10-trien-5-yl ester

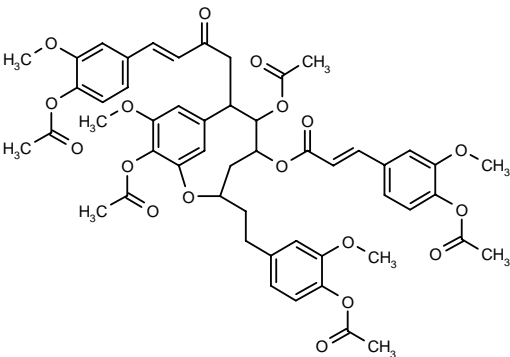


C42 H44 O13; Mol wt: 756.7966

ACTION – Matrix metalloproteinase (MMP) inhibitor isolated from *Curcuma longa* L. with *in vitro* activity against MMP-9 (gelatinase B), MMP-1 (collagenase 1) and MMP-3 (stromelysin 1). Potentially useful for the treatment of skin aging, as well as other diseases associated with abnormal metabolism of tissue matrix such as arthritis, tissue ulcers, metastasis and tumor infiltration, etc. Other exemplified compounds are:



317015: C42 H42 O13



317016: C52 H54 O18

SOURCE – Shiseido.

REFERENCES

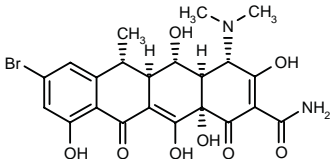
1. Okazaki, G. et al. (Shiseido Co. Ltd.) *Diaryl heptanoids and MMPs inhibitors*. JP 2002030081.

ANTIINFECTIVE THERAPY

ANTIBIOTICS

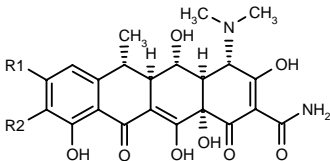
317402

(4*S*,4*aR*,5*S*,5*aR*,6*R*,12*aS*)-8-Bromo-4-(dimethylamino)-3,5,10,12,12*a*-pentahydroxy-6-methyl-1,11-dioxo-1,4,4*a*,5,5*a*,6,11,12*a*-octahydrotetracene-2-carboxamide



C22 H23 Br N2 O8; Mol wt: 523.3337

ACTION – Antibacterial agent with potential particularly for the treatment of infections caused by *Escherichia coli*, *Staphylococcus aureus* and *Enterococcus faecalis*. Other specifically claimed 8-substituted tetracycline compounds are:



Compound	R1	R2	Formula
317403	Ph	H	C ₂₈ H ₂₈ N ₂ O ₈
317404	4-NO2-Ph	H	C ₂₈ H ₂₇ N ₂ O ₁₀
317405	ethynyl	NH2	C ₂₄ H ₂₅ N ₃ O ₈
317406	Ph	NH2	C ₂₈ H ₂₉ N ₃ O ₈

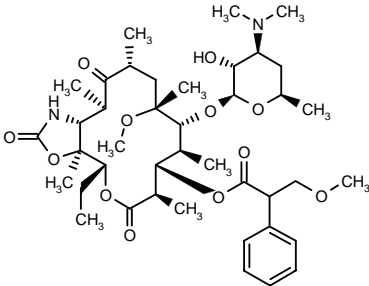
SOURCE – Tufts University, Boston, MA (US).

REFERENCES

1. Nelson, M. (Tufts University) *8-Substd. tetracycline cpds*. WO 0212170.

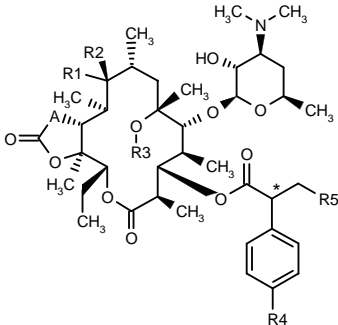
317786

11-Amino-11-deoxy-3-*O*-des(hexopyranosyl)-3-*O*-(3-methoxy-2-phenylpropionyl)-6-*O*-methylerythromycin A 11-*N*,12-*O*-cyclic carbamate

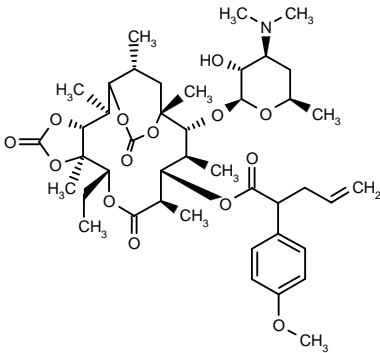


C41 H64 N2 O12; Mol wt: 776.9586

ACTION – Macrolide antibiotic, potentially useful for the treatment of bacterial and protozoal infections. Other exemplified 3-*O*-acyl-3-*O*-des(hexopyranosyl)erythromycin derivatives include the following:



Compound	R1	R2	R3	R4	R5	A	Isomer *	Formula
317787		-O-	Me	OMe	vinyl	NH		C ₄₃ H ₆₆ N ₂ O ₁₂
317788		-O-	Me	H	Ph	NH		C ₄₆ H ₆₆ N ₂ O ₁₁
317790	H	NH2	H	H	vinyl	O	R	C ₄₁ H ₆₄ N ₂ O ₁₁
317791	H	N(Me)2	H	H	OMe	O		C ₄₂ H ₆₈ N ₂ O ₁₂



317789: C43 H63 N O14

SOURCE – Pfizer.

REFERENCES

1. Chen, Y. and Su, W.-G. (Pfizer Products Inc.) *Macrolide antibiotics*. WO 0212260.

SOURCE – Shiseido.

REFERENCES

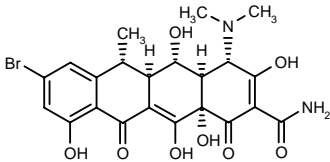
1. Okazaki, G. et al. (Shiseido Co. Ltd.) *Diaryl heptanoids and MMPs inhibitors*. JP 2002030081.

ANTIINFECTIVE THERAPY

ANTIBIOTICS

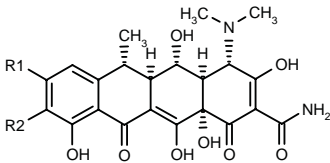
317402

(4*S*,4*aR*,5*S*,5*aR*,6*R*,12*aS*)-8-Bromo-4-(dimethylamino)-3,5,10,12,12*a*-pentahydroxy-6-methyl-1,11-dioxo-1,4,4*a*,5,5*a*,6,11,12*a*-octahydrotetracene-2-carboxamide



C22 H23 Br N2 O8; Mol wt: 523.3337

ACTION – Antibacterial agent with potential particularly for the treatment of infections caused by *Escherichia coli*, *Staphylococcus aureus* and *Enterococcus faecalis*. Other specifically claimed 8-substituted tetracycline compounds are:



Compound	R1	R2	Formula
317403	Ph	H	C ₂₈ H ₂₈ N ₂ O ₈
317404	4-NO2-Ph	H	C ₂₈ H ₂₇ N ₃ O ₁₀
317405	ethynyl	NH2	C ₂₄ H ₂₅ N ₃ O ₈
317406	Ph	NH2	C ₂₈ H ₂₉ N ₃ O ₈

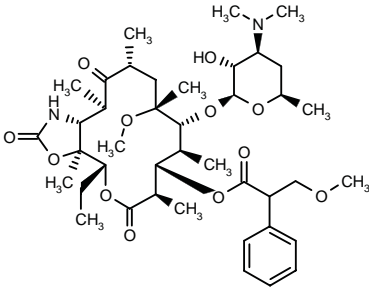
SOURCE – Tufts University, Boston, MA (US).

REFERENCES

1. Nelson, M. (Tufts University) *8-Substd. tetracycline cpds*. WO 0212170.

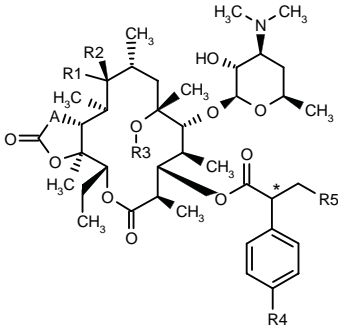
317786

11-Amino-11-deoxy-3-*O*-des(hexopyranosyl)-3-*O*-(3-methoxy-2-phenylpropionyl)-6-*O*-methylerythromycin A 11-*N*,12-*O*-cyclic carbamate

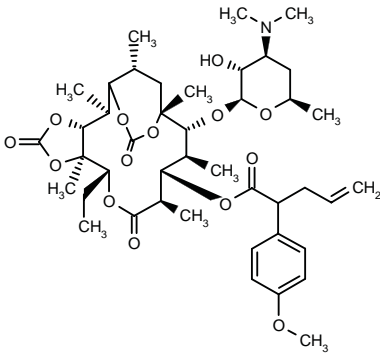


C41 H64 N2 O12; Mol wt: 776.9586

ACTION – Macrolide antibiotic, potentially useful for the treatment of bacterial and protozoal infections. Other exemplified 3-*O*-acyl-3-*O*-des(hexopyranosyl)erythromycin derivatives include the following:



Compound	R1	R2	R3	R4	R5	A	Isomer *	Formula
317787		-O-	Me	OMe	vinyl	NH		C ₄₃ H ₆₆ N ₂ O ₁₂
317788		-O-	Me	H	Ph	NH		C ₄₆ H ₆₆ N ₂ O ₁₁
317790	H	NH2	H	H	vinyl	O	R	C ₄₁ H ₆₄ N ₂ O ₁₁
317791	H	N(Me)2	H	H	OMe	O		C ₄₂ H ₆₈ N ₂ O ₁₂



317789: C43 H63 N O14

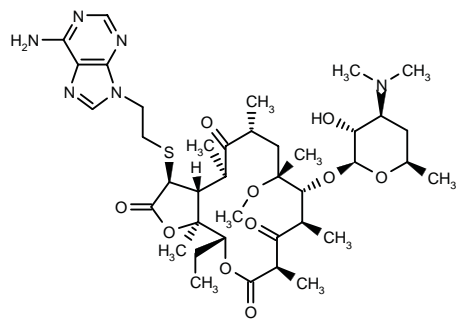
SOURCE – Pfizer.

REFERENCES

1. Chen, Y. and Su, W.-G. (Pfizer Products Inc.) *Macrolide antibiotics*. WO 0212260.

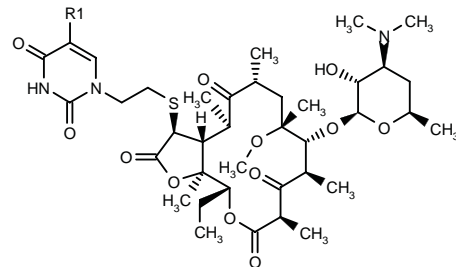
317885

(3*S*,3*aR*,4*R*,6*R*,8*R*,9*R*,10*R*,12*R*,15*R*,15*aS*)-3-[2-(6-Amino-9*H*-purin-9-yl)ethylsulfanyl]-9-[3-(dimethylamino)-3,4,6-trideoxy-β-D-xylo-hexopyranosyloxy]-15-ethyl-8-methoxy-4,6,8,10,12,15*a*-hexamethylperhydrofuro[2,3-*c*]oxacyclotetradecin-2,5,11,13-tetraone



C39 H60 N6 O10 S; Mol wt: 805.0010

ACTION – Macrolide antibiotic with *in vitro* activity against a panel of bacteria including many strains of *Haemophilus influenzae*. Other exemplified compounds are:



Compound	R1	Formula
317890	Me	C ₃₉ H ₆₁ N ₃ O ₁₂ S
317891	H	C ₃₈ H ₅₉ N ₃ O ₁₂ S

SOURCE – Basilea Pharmaceutica.

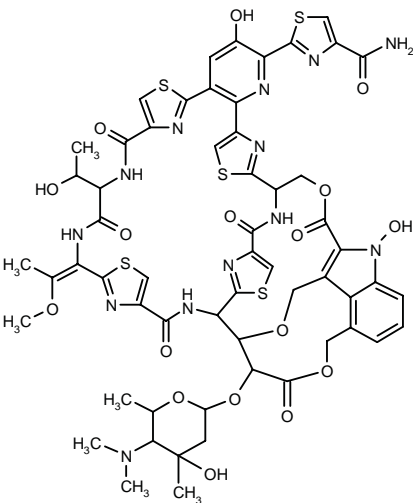
REFERENCES

1. Angehrn, P. et al. (Basilea Pharmaceutica AG) *New macrolides with antibacterial activity*. WO 0216380.

NOCATHIACIN IV

317581

2-(4-Carbamoylthiazol-2-yl)-49-[5-(dimethylamino)-4-hydroxy-4,6-dimethyltetrahydropyran-2-yloxy]-3,29-dihydroxy-11-(1-hydroxyethyl)-14-(1-methoxyethylidene)-10,11,12,13,14,19,20,21,22,24,29,30,32,33-tetradecahydro-9*H*-22,25-(ethanoxymethano)-8,5:18,15:37,34-trinitrilo-21,33-([2,4]-*endo*-thiazolo-methanimino)pyrido[3',2':20,21][1,28,8,18,24,4,11,14]-dioxatrithiatrizacyclodotriacontino[30,31-*b*]indole-9,12,19,30,40,48-hexaone



C58 H57 N13 O17 S5; Mol wt: 1368.4920

ACTION – Nocathiacin derivative with antibacterial activity. Nocathiacin IV demonstrated activity against a panel of bacterial strains, with MIC values below 0.1 μg/ml. *In vivo*, the compound gave a PD₅₀ of 1.07 mg/kg s.c. in a mouse model of systemic infection caused by *Staphylococcus aureus* A15090.

SOURCE – Bristol-Myers Squibb.

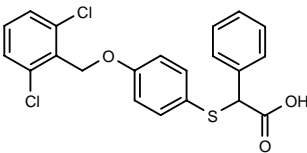
REFERENCES

1. Li, W. et al. (Bristol-Myers Squibb Co.) *Nocathiacin antibiotics prepared by biotransformation or chemical methods*. WO 0213834.

ANTIBACTERIAL DRUGS

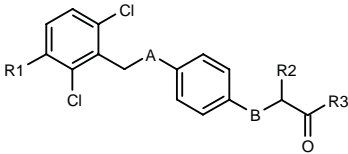
317155

2-[4-(2,6-Dichlorobenzyloxy)phenylsulfanyl]-2-phenylacetic acid



C21 H16 Cl2 O3 S; Mol wt: 419.3264

ACTION – Fatty acid synthase FabH inhibitor, reported to be useful for the treatment of Gram-positive and Gram-negative bacterial infections. Other exemplified compounds include the following:



Compound	R1	R2	R3	A	B	Formula
317156	H	Ph	2,3,4-(F)3-PhNH	O	S	C ₂₇ H ₁₈ Cl ₂ F ₃ NO ₂ S
317157	H	Ph	4-morpholinyl-(CH ₂) ₃ NH	O	S	C ₂₈ H ₃₀ Cl ₂ N ₂ O ₃ S
317158	H	Ph	5-tetrazolyl-CH ₂ CH ₂ NH	O	S	C ₂₄ H ₂₁ Cl ₂ N ₅ O ₂ S
317159	H	Ph	1-CO ₂ H-cyclohexyl-NH	O	S	C ₂₈ H ₂₇ Cl ₂ NO ₄ S
317160	H	Ph	5-NH ₂ -2-tetrazolyl-CH ₂ CH ₂ NH	O	S	C ₂₄ H ₂₂ Cl ₂ N ₆ O ₂ S
317161	H	3-thienyl	5-tetrazolyl-NH	O	S	C ₂₀ H ₁₅ Cl ₂ N ₅ O ₂ S ₂
317162	H	Ph	OH	S	O	C ₂₁ H ₁₆ Cl ₂ O ₃ S
317163	OH	Ph	OH	O	S	C ₂₁ H ₁₆ Cl ₂ O ₄ S

SOURCE – GlaxoSmithKline.

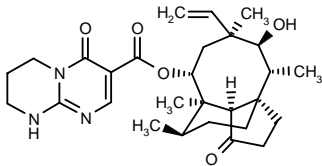
REFERENCES

1. Christensen, S.B. IV et al. (GlaxoSmithKline Inc.) *Fatty acid synthase inhibitors*. WO 0209651.

317393

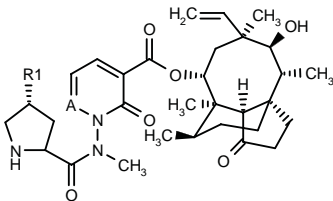
6-Oxo-2,3,4,6-tetrahydro-1*H*-pyrimido[1,2-*a*]pyrimidine-7-carboxylic acid (3*aS*,4*R*,5*S*,6*S*,8*R*,9*R*,9*aR*,10*R*)-5-hydroxy-4,6,9,10-tetramethyl-1-oxo-6-vinylperhydro-3*a*,9-propanocyclopentacycloocten-8-yl ester

14-*O*-(6-Oxo-2,3,4,6-tetrahydro-1*H*-pyrimido[1,2-*a*]pyrimidine-7-ylcarbonyl)mutilin

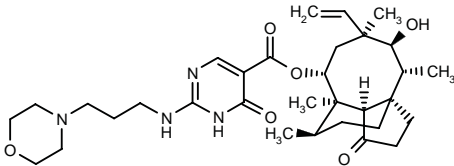


C28 H39 N3 O5; Mol wt: 497.6321

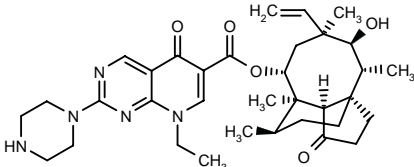
ACTION – Antibacterial mutilin ester for use in the treatment of recurrent otitis media, recurrent acute bacterial sinusitis, skin and soft tissue infections and acne. Other specifically claimed compounds are:



Compound	R1	A	Isomer	Formula
317397	H	N	D	C ₃₁ H ₄₄ N ₄ O ₆
317398	H	CH	D	C ₃₂ H ₄₅ N ₃ O ₆
317399	H	N	L	C ₃₁ H ₄₄ N ₄ O ₆
317400	OMe	N	L	C ₃₂ H ₄₆ N ₄ O ₇



317394: C32 H48 N4 O6



317395: C34 H47 N5 O5

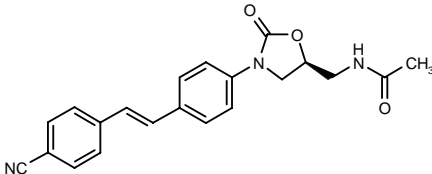
SOURCE – GlaxoSmithKline.

REFERENCES

1. Aitken, S. et al. (GlaxoSmithKline plc) *Heterocyclic mutilin esters and their use as antibacterials*. WO 0212199.

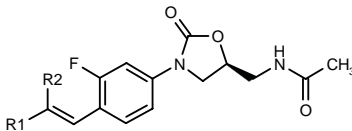
318278

N-[3-[4-[(*E*)-2-(4-Cyanophenyl)vinyl]phenyl]-2-oxooxazolidin-5(*S*)-ylmethyl]acetamide



C21 H19 N3 O3; Mol wt: 361.3991

ACTION – Antibacterial 2-oxazolidinone compound, potentially useful for the treatment of bacterial infections, psoriasis, arthritis and toxicity associated with chemotherapy. Other exemplified compounds include the following:



Compound	R1	R2	Isomer	Formula
318280	5-Ac-2-thienyl	Br	Z	C ₂₀ H ₁₈ BrFN ₂ O ₄ S
318281	3-Ac-Ph	Br	Z	C ₂₂ H ₂₀ BrFN ₂ O ₄
318283	(<i>E</i>)-4-(CO ₂ HCH=CH)-Ph	Br	Z	C ₂₃ H ₂₀ BrFN ₂ O ₅
318284	3-Pyr	H	E	C ₁₉ H ₁₈ FN ₃ O ₃
318285	3-Pyr	F	Z	C ₁₉ H ₁₇ F ₂ N ₃ O ₃
318288	2-CN-3-thienyl	F	Z	C ₁₉ H ₁₅ F ₂ N ₃ O ₃ S
318289	3-NH ₂ -Ph	Br	Z	C ₂₀ H ₁₉ BrFN ₃ O ₃
318290	3-(NH ₂ CO)-Ph	Br	Z	C ₂₁ H ₁₉ BrFN ₃ O ₄

SOURCE – Abbott.

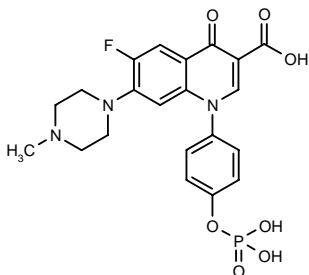
REFERENCES

1. Wiedeman, P.E. et al. (Abbott Laboratories Inc.) *Oxazolidinones and their use as antibacterial agents*. WO 0218354.

PA-2808

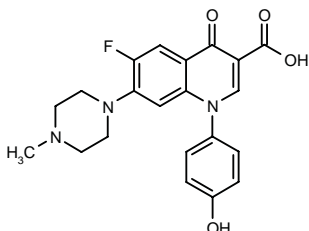
318292

6-Fluoro-7-(4-methylpiperazin-1-yl)-4-oxo-1-[4-(phosphonooxy)phenyl]-1,4-dihydroquinoline-3-carboxylic acid



C21 H21 F N3 O7 P; Mol wt: 477.3829

ACTION – Antibacterial quinolone giving MIC values of 0.4 µg/ml against *Staphylococcus aureus* and *Escherichia coli* strains. Compound acted as a prodrug and was transformed to the corresponding active compound **PA-2789** by exposure to purified alkaline phosphatase or rat lung homogenates, as well as in an isolated perfused rat lung model. In a rat model of *E. coli*-induced pneumonia, PA-2808 showed significant efficacy at an i.v. dose of 5 mg/kg. In a mouse model of *E. coli* acute systemic infection, the prodrug gave an ED₅₀ value of 0.74 mg/kg i.v.



PA-2789 [318293]: C21 H20 F N3 O4

SOURCE – Chiron.

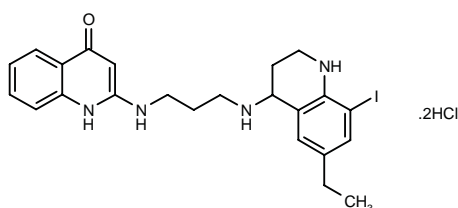
REFERENCES

1. Baker, W.R. et al. (Chiron Corp.) *Quinoline antibacterial cpds. and methods of use thereof*. WO 0218345.

SB-425076*

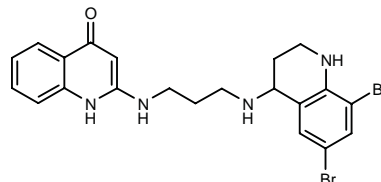
289018

2-[3-(6-Ethyl-8-iodo-1,2,3,4-tetrahydroquinolin-4-yl)-amino]propylamino]quinolin-4(1*H*)-one dihydrochloride



C23 H27 I N4 O . 2HCl; Mol wt: 575.3151

ACTION – Antibacterial agent, an inhibitor of *Staphylococcus aureus* methionyl-tRNA synthetase (methionine—tRNA ligase; IC₅₀ = 1.4-12 nM) with high selectivity over rat liver enzyme. It showed antibacterial activity against Gram-positive bacteria including laboratory strains and clinical isolates of *S. aureus*, *Staphylococcus epidermidis*, *Enterococcus faecalis* and *Enterococcus faecium* (MIC₉₀ < 1 µg/ml), and it was also active against some strains of *Streptococcus pneumoniae*. In an *S. aureus*-induced groin abscess infection in rats, compound significantly reduced bacterial counts at a dose of 21 mg/kg i.v. and showed the same efficacy as erythromycin at 50 mg/kg i.v. Another related compound is:



SB-362916 [289013]:** C21 H22 Br2 N4 O

SOURCE – GlaxoSmithKline.

REFERENCES

1. Berge, J.M. et al. (GlaxoSmithKline plc) *Quinolones as t-RNA synthetase inhibitors and antibacterial agents*. WO 0021949.

2. Jarvest, R.L. et al. *Nanomolar inhibitors of Staphylococcus aureus methionyl tRNA synthetase with potent antibacterial activity against Gram-positive pathogens*. J Med Chem 2002, 45(10): 1959.

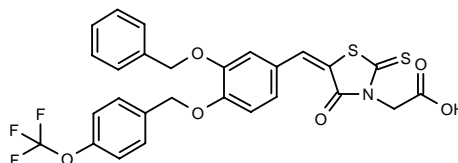
*Identified compound **289018** (see **289011**) Drug Data Rep 2000, 022(08): 0722.

Identified compound **289013 (see **289011**) Drug Data Rep 2000, 022(08): 0722.

ANTIFUNGAL AGENTS

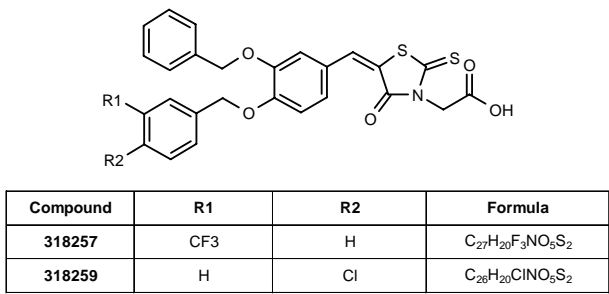
318256

2-[5-[3-(Benzyloxy)-4-[4-(trifluoromethoxy)benzyloxy]-benzylidene]-4-oxo-2-thioxothiazolidin-3-yl]acetic acid



C27 H20 F3 N O6 S2; Mol wt: 575.5820

ACTION – Antifungal agent proven to inhibit *Candida albicans* PMT-1 enzyme with an IC₅₀ of 1 µM, and shown to sensitize *C. albicans* SC5314 to geneticin (IC₅₀ = 0.35 µM in the presence of test compound), thus confirming its PMT-1-inhibitory activity in a cell-based assay. Particularly useful for the treatment of topical, mucosal and systemic infections caused by *Candida*, *Trichophyton*, *Microsporum*, *Cryptococcus neoformans*, *Aspergillus fumigatus*, *Coccidioides*, *Paracoccidioides*, *Histoplasma*, *Blastomyces*, and *Epidermophyton* species. Other exemplified 5-benzylidenethiazolidine-2,4-dione derivatives are:



SOURCE – Oxford GlycoSciences.

REFERENCES

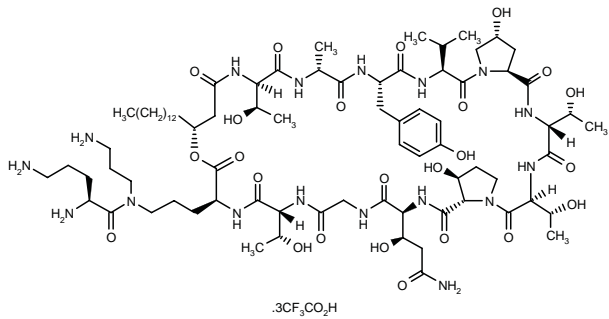
1. Orchard, M.G. et al. (Oxford GlycoSciences Ltd.) *Benzylidene thiazolidinediones and their use as antimycotic agents*. WO 0217915.

BAL-8349¹⁻⁴

318143

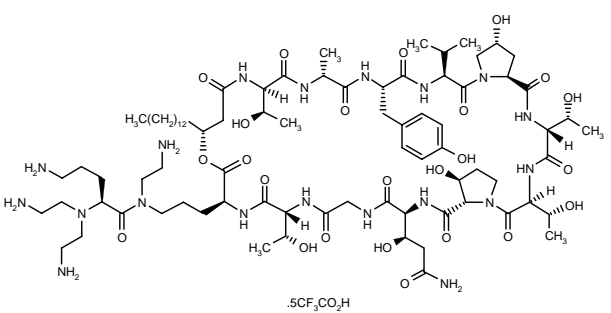
Cyclo[D-alanyl-L-tyrosyl-L-valyl-4(R)-hydroxy-L-prolyl-D-allothreonyl-L-threonyl-3(S)-hydroxy-L-prolyl-3(R)-hydroxy-L-glutaminyglycyl-D-allothreonyl-N-δ-(3-aminopropyl)-N^δ-(L-ornithyl)-L-ornithyl-3(R)-hydroxy-hexadecanoyl-D-allothreonyl] tris(trifluoroacetate)

Ro-0098349



C79 H133 N17 O24 . 3 C2 H F3 O2; Mol wt: 2047.0800

ACTION – Antifungal agent, a water-soluble derivative of a macrocyclic depsipeptide (Ro-0093655) isolated from the culture broth of *Deuteromycotina* spp., with potent inhibitory activity against 1,3-β-glucan synthase (IC₅₀ = 0.83 nM) and a broad antifungal spectrum against *Candida* spp. (including fluconazole-resistant strains) and *Aspergillus fumigatus*. Compound exhibited higher antifungal activity than the parent compound in models of pulmonary aspergillosis and systemic candidiasis in mice (ED₅₀ = 5.2 and 0.05 mg/kg i.v., respectively). Discrete bioavailability (15-20%) was seen in monkeys after intranasal administration, a more convenient formulation for the treatment of systemic fungal infections. Another related compound is:



BAL-1198 [307599]¹⁻⁵: C82 H141 N19 O24 . 5 C2 H F3 O2
Ro-0791198

SOURCES – Basilea Pharmaceutica; Roche.

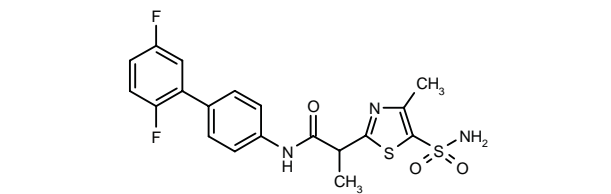
REFERENCES

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- 2. Kohchi, M. et al. (Basilea Pharmaceutica AG) *Novel cyclic cpds*. WO 0153322.
- 3. Masubuchi, K. et al. *Synthesis and antifungal activities of novel 1,3-β-D-glucan synthase inhibitor. Part 2*. Bioorg Med Chem Lett 2001, 11(10): 1273.
- 4. Okada, T. et al. *Synthesis and antifungal activities of novel 1,3-β-D-glucan synthase inhibitors*. 223rd ACS Natl Meet (April 7-11, Orlando) 2002, Abst MEDI 174.
- 5. *Company Profile: Basilea Pharmaceutica*. DailyDrugNews.com (Daily Essentials) 2002, Feb 6.

ANTIVIRAL DRUGS

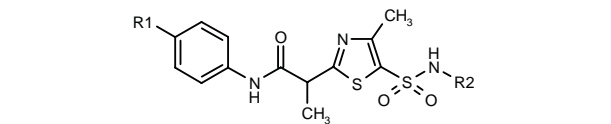
317133

N-(2',5'-Difluorobiphenyl-4-yl)-2-(4-methyl-5-sulfamoylthiazol-2-yl)propionamide



C19 H17 F2 N3 O3 S2; Mol wt: 437.4893

ACTION – Antiviral agent, particularly useful for the treatment of infections caused by herpes simplex virus (HSV); it displayed IC₅₀ values of 0.05 and 0.01 μM, respectively, against HSV-1 F/Vero and HSV-2 G/Vero strains, compared to IC₅₀ values of 1 and 3 μM, respectively, for aciclovir. Other exemplified thiazole-5-sulfonamide derivatives include the following:

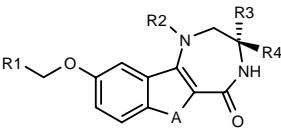


Compound	R1	R2	Formula
317134	Ph	H	C ₁₉ H ₁₉ N ₃ O ₃ S ₂
317135	2-Pyr	H	C ₁₈ H ₁₈ N ₄ O ₃ S ₂
317136	OEt	H	C ₁₅ H ₁₉ N ₃ O ₄ S ₂
317137	Ph	Me	C ₂₀ H ₂₁ N ₃ O ₃ S ₂

SOURCE – Bayer.

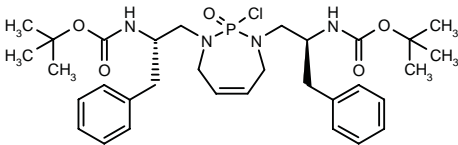
REFERENCES

1. Hendrix, M. et al. (Bayer AG) *Inverse thiazolyl amide derivs.* DE 10038022, WO 0212211.



317678

1,3-Bis[2(S)-(tert-butoxycarbonylamino)-3-phenylpropyl]-2-chloro-2,3,4,7-tetrahydro-1H-1,3,2-diazaphosphepine 2-oxide



C32 H46 Cl N4 O5 P; Mol wt: 633.1654

ACTION – A representative compound from a series of amino acid-derived cyclic phosphonamides that inhibits herpes simplex virus (HSV) and HIV proteases. The compound inhibited HSV protease by 44.4% at 200 μM and HIV protease by 23% at 99 μM, and it was also found to inhibit human cathepsin K by 34% inhibition at 106 μM.

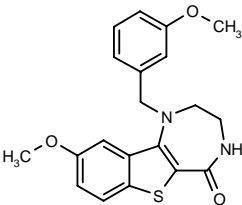
SOURCE – University of Kansas, Lawrence, KS (US).

REFERENCES

1. Hanson, P.R. et al. (University of Kansas) *Amino acid-derived cyclic phosphonamides and methods of synthesizing the same.* WO 0214344.

317754

9-Methoxy-1-(3-methoxybenzyl)-2,3,4,5-tetrahydro-1H-[1]benzothieno[3,2-e][1,4]diazepin-5-one



C20 H20 N2 O3 S; Mol wt: 368.4550

ACTION – Antiviral agent for the treatment of herpesvirus infections with an improved therapeutic index and metabolic stability. Particularly useful for the treatment of infections caused by herpes simplex virus (HSV), cytomegalovirus (CMV) and varicella-zoster virus (VZV). When tested against HSV-1, the compound displayed EC₅₀ and TC₅₀ values of 0.0002 and 10 μM, respectively, for a therapeutic index of 50,000. Other exemplified diazepinones include the following:

Compound	R1	R2	R3	R4	A	Formula
317755	H	H	H	H	S	C ₁₂ H ₁₂ N ₂ O ₂ S
317757	H	Et	H	H	O	C ₁₄ H ₁₆ N ₂ O ₃
317758	H	4-MeO-PhCH2	Me	Me	S	C ₂₂ H ₂₄ N ₂ O ₃ S
317760	Me	H	Me	Me	S	C ₁₅ H ₁₈ N ₂ O ₂ S
317761	H	3-MeO-PhCH2	Me	H	S	C ₂₁ H ₂₂ N ₂ O ₃ S
317762	H	CH2C(Cl)=CH2	H	H	S	C ₁₆ H ₁₇ ClN ₂ O ₂ S

SOURCES – Japan Tobacco; Pfizer.

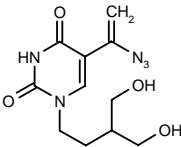
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1. Cho, H. et al. (Pfizer Inc.;Japan Tobacco Inc.) *Diazepinones as antiviral agents.* WO 0214324.

318990

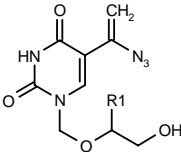
5-(1-Azidovinyl)-1-[4-hydroxy-3-(hydroxymethyl)butyl]-pyrimidine-2,4(1H,3H)-dione

5-(1-Azidovinyl)-1-[4-hydroxy-3-(hydroxymethyl)butyl]-uracil



C11 H15 N5 O4; Mol wt: 281.2705

ACTION – Antiviral agent, a potent and selective inhibitor of duck hepatitis B virus (EC₅₀ = 0.01-0.05 μg/ml in primary duck hepatocyte cultures) with no cytotoxic activity at up to 100 μg/ml against Vero cells and human foreskin fibroblasts. Other related acyclic pyrimidine nucleosides are:



Compound	R1	Formula
318988	H	C ₉ H ₁₁ N ₅ O ₄
318989	CH2OH	C ₁₀ H ₁₃ N ₅ O ₅

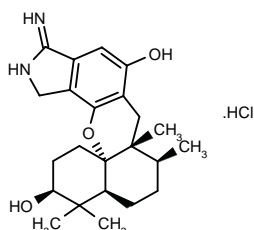
SOURCE – University of Alberta, Edmonton, AB (CA).

REFERENCES

1. Kumar, R. et al. *Design and synthesis of novel 5-substituted acyclic pyrimidine nucleosides as potent and selective inhibitors of hepatitis B virus.* J Med Chem 2002, 45(10): 2032.

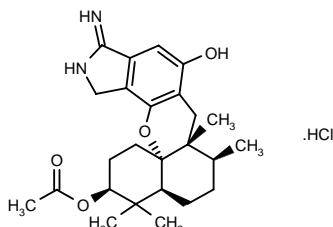
319170

(6a*R*,7*S*,9a*S*,11*S*,13a*S*)-3-Imino-6a,7,10,10-tetramethyl-2,3,6,6a,7,8,9,9a,10,11,12,13-dodecahydro-1*H*-naphtho[1',8a':5,6]pyran[2,3-*e*]isoindole-5,11-diol hydrochloride



C23 H32 N2 O3 . HCl; Mol wt: 420.9777

ACTION – Agent for influenza A virus, a derivative of stachyflin, an antiviral agent isolated from the fermentation of *Stachybotrys* sp. RF-7260 that inhibits the fusion processes between the viral envelope and the host cell membrane. The derivative exhibited antiviral activity comparable to the parent compound ($IC_{50} = 2$ and 3 nM, respectively, against the A/WSN/33[H1N1] strain of influenza A virus), but showed superior water solubility. Another related compound is:



SQ-02-S-V2 [317846]: C25 H34 N2 O4 . HCl

SOURCE – Shionogi.

REFERENCES

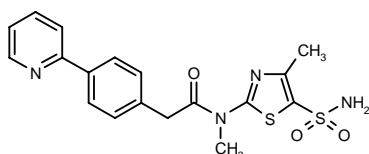
1. Kamigauchi, T. et al. (Shionogi & Co. Ltd.) *Sesquiterpene derivs. having antiviral activity*. EP 0855398, WO 9711947.

2. Ninagawa, K. et al. *Novel stachyflin derivatives from Stachybotrys sp. RF-7260 fermentation, isolation, structure elucidation and biological activities*. J Antibiot 2002, 55(3): 239.

BAY-57-1293

318199

N-[5-(Aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-*N*-methyl-2-(4-pyridin-2-ylphenyl)acetamide



C18 H18 N4 O3 S2; Mol wt: 402.4972

ACTION – Antiviral agent, an inhibitor of the helicase–primase enzyme complex with activity against herpes simplex virus (HSV). Compound was nearly 2 orders of magnitude more potent than aciclovir *in vitro* against HSV-1 ($IC_{50} = 0.02$ and 1 μ M, respectively) and HSV-2 ($IC_{50} = 0.02$ and 4 μ M, respectively), and it retained strong activity against aciclovir-resistant HSV-1 ($IC_{50} = 0.02$ μ M). In a murine model of disseminated HSV-1 infection, compound was at least 10-fold more potent than valaciclovir and aciclovir ($ED_{50} = 0.5$, 17 and 22 mg/kg p.o. t.i.d., respectively) and it was also active when applied once daily. In a guinea pig model of intravaginal HSV-2 infection, compound (20 mg/kg p.o. b.i.d.) completely suppressed clinical symptoms of primary disease, viral shedding and prevented recurrent disease symptoms in the follow-up period.

SOURCE – Bayer.

REFERENCES

1. Fischer, R. et al. (Bayer AG) *Thiazolyl amide derivs*. DE 19962532, WO 0147904.

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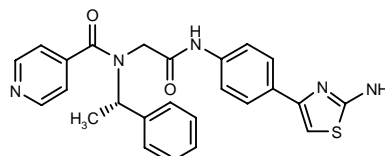
3. Kleymann, G. et al. (Bayer AG) *Method for identifying cpds. with anti-herpes activity*. WO 0196874.

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BILS-179BS

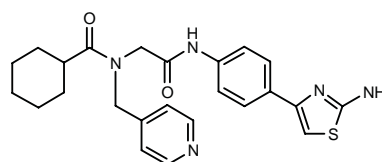
318202

N-[*N*-[4-(2-Aminothiazol-4-yl)phenyl]carbamoylmethyl]-*N*-[1(*S*)-phenylethyl]pyridine-4-carboxamide



C25 H23 N5 O2 S; Mol wt: 457.5557

ACTION – Non-nucleoside antiviral agent, an inhibitor of the herpes simplex virus (HSV) helicase–primase complex ($IC_{50} = 1.3$, 0.15 and 0.43 μ M for inhibition of DNA helicase, RNA polymerase [primase] and DNA-dependent ATPase, respectively), with potent *in vitro* activity against HSV-1 ($EC_{50} = 0.027$ μ M); it was also active against nucleoside-resistant strains ($EC_{50} = 0.08$ - 0.15 μ M). *In vivo*, compound was orally active in mouse models of cutaneous HSV-1 disease ($ED_{50} = 31$ mg/kg/day for reduction of peak and overall disease scores) and HSV-2 genital disease ($ED_{50} = 46$ mg/kg/day for reduction of mean disease score). Another related compound is:



BILS-103BS [318803]: C24 H27 N5 O2 S

SOURCE – Boehringer Ingelheim.

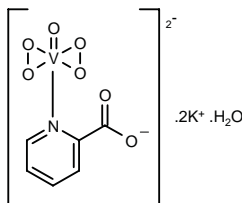
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2. Crute, J.J. et al. (Boehringer Ingelheim [Canada] Ltd.;Boehringer Ingelheim Pharmaceuticals Inc.) *Phenyl thiazole derivs. with anti-herpes virus properties*. EP 0871619, JP 2000502702, US 6057451, WO 9724343.
3. Crute, J.J. et al. *Herpes simplex virus helicase-primase inhibitors are active in animal models of human disease*. Nat Med 2002, 8(4): 386.

AIDS MEDICINES

317189

Dipotassium oxodiperoxy(pyridine-2-carboxylato)vana-
date(2–)hydrate



C₆ H₄ K₂ N O₇ V . H₂O; Mol wt: 349.2504

ACTION – A representative bis(peroxo)vanadium compound with the ability to increase the antimicrobial efficacy of antiinfective agents. Such a compound is expected to be useful for the treatment of infections caused by viruses, particularly HIV. It was able to decrease HIV infectivity *in vitro* against a panel of cell lines. In addition, this compound showed additive antiviral effects when combined with nucleoside reverse transcriptase inhibitors such as AZT (zidovudine) and 3TC (lamivudine).

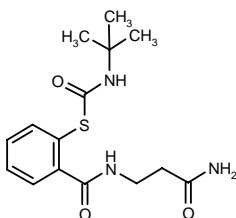
SOURCE – Virocell.

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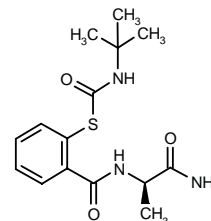
317287

N-[2-(*N*-*tert*-Butylcarbamoylsulfanyl)benzoyl]-β-alanin-
amide



C₁₅ H₂₁ N₃ O₃ S; Mol wt: 323.4149

ACTION – Anti-HIV-1 agent, an inhibitor of nucleocapsid p7 protein (NCp7) zinc finger domains of HIV-1 virus with antiviral activity in HIV-1-infected CEM-SS cells, human peripheral blood mononuclear cells and human monocytes (IC₅₀ = 0.37, 0.8 and 28.7 μM, respectively) and low cytotoxic activity (IC₅₀ = 142 μM). Another related compound is:



317286: C₁₅ H₂₁ N₃ O₃ S

SOURCES – Achillion; National Institutes of Health, Bethesda, MD (US); Southern Research Institute, Birmingham, AL (US).

REFERENCES

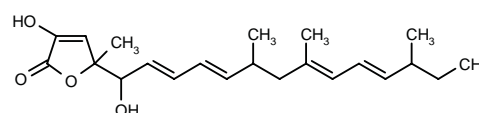
1. Goel, A. et al. *Benzamide-based thiocarbamates: A new class of HIV-1 NCp7 inhibitors*. Bioorg Med Chem Lett 2002, 12(5): 767.

TREATMENT OF HELMINTHIC DISEASES

FT-0554A

318262

3-Hydroxy-5-[1-hydroxy-6,8,12-trimethyltetradeca-
2(*E*),4(*E*),8(*E*),10(*E*)-tetraenyl]-5-methylfuran-2(5*H*)-one



C₂₂ H₃₂ O₄; Mol wt: 360.4908

ACTION – Anthelmintic agent prepared from the structurally related compound FT-0554, previously isolated from cultures of *Aspergillus niger* FT-0554 (FERM BP-6443). Title compound was shown to inhibit NADH-fumaric acid reductase from the mitochondrial fraction of *Ascaris lumbricoides* with an IC₅₀ of 0.4 μM.

SOURCE – Kitasato Institute, Tokyo (JP).

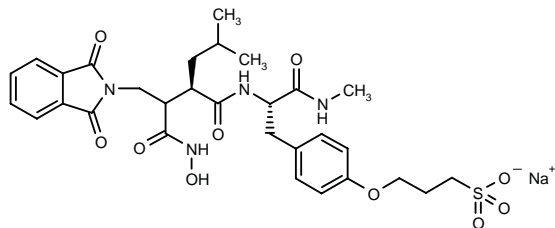
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TREATMENT OF SEPTIC SHOCK

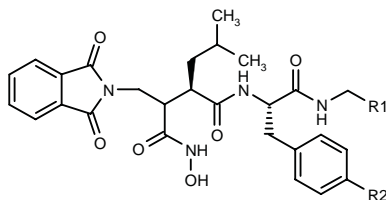
317054

N-[2(*R*)-[2-(1,3-Dioxo-2,3-dihydro-1*H*-isoindol-2-yl)-1-(*N*-hydroxycarbamoyl)ethyl]-4-methylpentanoyl]-4-*O*-(3-sulfopropyl)-L-tyrosine methylamide sodium salt

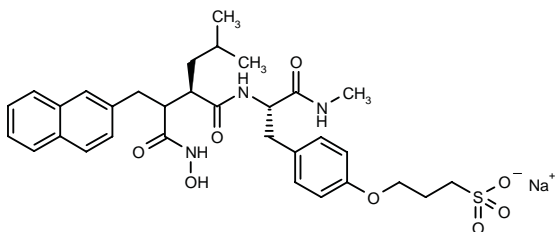


C30 H37 N4 Na O10 S; Mol wt: 668.6963

ACTION – Lipopolysaccharide (LPS) inhibitor shown to reduce the concentration of LPS in the blood and abdomen following i.v. administration at 5 mg/kg/h in a rat model of peritonitis. Potentially useful for the treatment of sepsis, multiple organ failure, chronic rheumatoid arthritis, Crohn’s disease, cachexia, myasthenia gravis, systemic erythematosis, asthma, type 1 diabetes and psoriasis, among other inflammatory and autoimmune diseases. Other exemplified sulfonic acid derivatives are:



Compound	R1	R2	Formula
317060	H	OCH2CH2SO3Na	C ₂₉ H ₃₅ N ₄ NaO ₁₀ S
317061	H	O(CH2)4SO3Na	C ₃₁ H ₃₉ N ₄ NaO ₁₀ S
317064	SO3Na	H	C ₂₇ H ₃₁ N ₄ NaO ₉ S
317065	CH2SO3Na	H	C ₂₈ H ₃₃ N ₄ NaO ₉ S
317066	CH2CH2SO3Na	H	C ₂₉ H ₃₅ N ₄ NaO ₉ S
317067	(CH2)3SO3Na	H	C ₃₀ H ₃₇ N ₄ NaO ₉ S
317068	(CH2)4SO3Na	H	C ₃₁ H ₃₉ N ₄ NaO ₉ S



317063: C32 H40 N3 Na O8 S

SOURCE – Mitsubishi Pharma.

REFERENCES

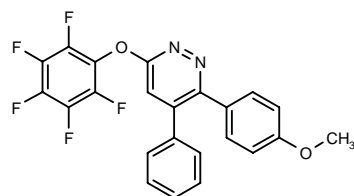
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TREATMENT OF MUSCULOSKELETAL AND CONNECTIVE TISSUE DISEASES

ANTIARTHRITIC DRUGS

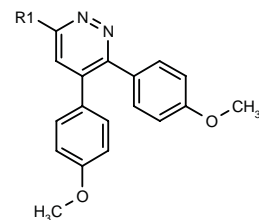
317004

3-(4-Methoxyphenyl)-6-(pentafluorophenoxy)-4-phenylpyridazine



C23 H13 F5 N2 O2; Mol wt: 444.3577

ACTION – IL-1β production inhibitor proven to inhibit lipopolysaccharide (LPS)-stimulated IL-1β production in HL-60 cells with an IC₅₀ of 0.01 μM. Potentially useful for the treatment of rheumatism, immunodeficiency syndrome, arthritis, inflammatory colitis, ischemic cardiopathy, encephalopathy, nephritis and hepatitis, type 1 diabetes, arteriosclerosis, Parkinson’s disease, Alzheimer’s disease and leukemia. Other exemplified phenylpyridazine derivatives are:



Compound	R1	Formula
317005	OPh	C ₂₄ H ₂₀ N ₂ O ₃
317006	2,3-(F)2-PhO	C ₂₄ H ₁₈ F ₂ N ₂ O ₃
317007	2,5-(F)2-PhO	C ₂₄ H ₁₈ F ₂ N ₂ O ₃
317008	2,3,5,6-(F)4-PhO	C ₂₄ H ₁₆ F ₄ N ₂ O ₃
317009	(F)5-PhO	C ₂₄ H ₁₅ F ₅ N ₂ O ₃
317010	2-CN-PhO	C ₂₅ H ₁₉ N ₃ O ₃
317012	3-CN-PhO	C ₂₅ H ₁₉ N ₃ O ₃
317014	CN	C ₁₉ H ₁₅ N ₃ O ₂

SOURCE – Kowa.

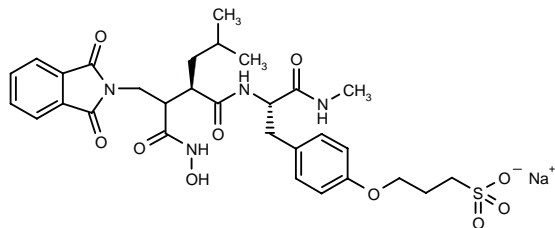
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TREATMENT OF SEPTIC SHOCK

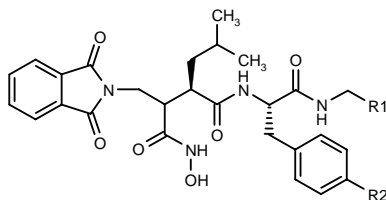
317054

N-[2(*R*)-[2-(1,3-Dioxo-2,3-dihydro-1*H*-isoindol-2-yl)-1-(*N*-hydroxycarbamoyl)ethyl]-4-methylpentanoyl]-4-*O*-(3-sulfopropyl)-L-tyrosine methylamide sodium salt

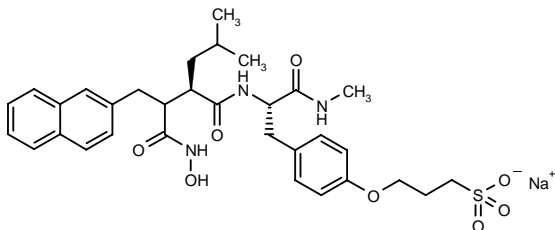


C30 H37 N4 Na O10 S; Mol wt: 668.6963

ACTION – Lipopolysaccharide (LPS) inhibitor shown to reduce the concentration of LPS in the blood and abdomen following i.v. administration at 5 mg/kg/h in a rat model of peritonitis. Potentially useful for the treatment of sepsis, multiple organ failure, chronic rheumatoid arthritis, Crohn’s disease, cachexia, myasthenia gravis, systemic erythematosis, asthma, type 1 diabetes and psoriasis, among other inflammatory and autoimmune diseases. Other exemplified sulfonic acid derivatives are:



Compound	R1	R2	Formula
317060	H	OCH2CH2SO3Na	C ₂₉ H ₃₅ N ₄ NaO ₁₀ S
317061	H	O(CH2)4SO3Na	C ₃₁ H ₃₉ N ₄ NaO ₁₀ S
317064	SO3Na	H	C ₂₇ H ₃₁ N ₄ NaO ₉ S
317065	CH2SO3Na	H	C ₂₈ H ₃₃ N ₄ NaO ₉ S
317066	CH2CH2SO3Na	H	C ₂₉ H ₃₅ N ₄ NaO ₉ S
317067	(CH2)3SO3Na	H	C ₃₀ H ₃₇ N ₄ NaO ₉ S
317068	(CH2)4SO3Na	H	C ₃₁ H ₃₉ N ₄ NaO ₉ S



317063: C32 H40 N3 Na O8 S

SOURCE – Mitsubishi Pharma.

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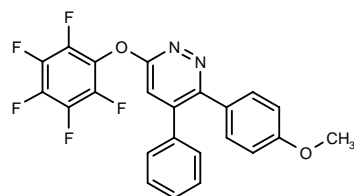
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TREATMENT OF MUSCULOSKELETAL AND CONNECTIVE TISSUE DISEASES

ANTIARTHRITIC DRUGS

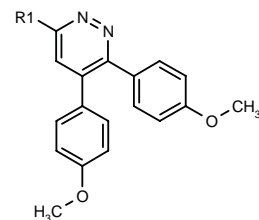
317004

3-(4-Methoxyphenyl)-6-(pentafluorophenoxy)-4-phenylpyridazine



C23 H13 F5 N2 O2; Mol wt: 444.3577

ACTION – IL-1β production inhibitor proven to inhibit lipopolysaccharide (LPS)-stimulated IL-1β production in HL-60 cells with an IC₅₀ of 0.01 μM. Potentially useful for the treatment of rheumatism, immunodeficiency syndrome, arthritis, inflammatory colitis, ischemic cardiopathy, encephalopathy, nephritis and hepatitis, type 1 diabetes, arteriosclerosis, Parkinson’s disease, Alzheimer’s disease and leukemia. Other exemplified phenylpyridazine derivatives are:



Compound	R1	Formula
317005	OPh	C ₂₄ H ₂₀ N ₂ O ₃
317006	2,3-(F)2-PhO	C ₂₄ H ₁₈ F ₂ N ₂ O ₃
317007	2,5-(F)2-PhO	C ₂₄ H ₁₈ F ₂ N ₂ O ₃
317008	2,3,5,6-(F)4-PhO	C ₂₄ H ₁₆ F ₄ N ₂ O ₃
317009	(F)5-PhO	C ₂₄ H ₁₅ F ₅ N ₂ O ₃
317010	2-CN-PhO	C ₂₅ H ₁₉ N ₃ O ₃
317012	3-CN-PhO	C ₂₅ H ₁₉ N ₃ O ₃
317014	CN	C ₁₉ H ₁₅ N ₃ O ₂

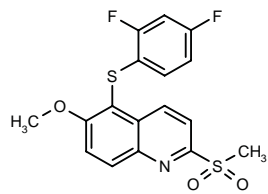
SOURCE – Kowa.

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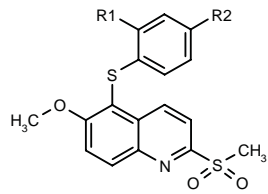
317138

5-(2,4-Difluorophenylsulfanyl)-6-methoxy-2-(methylsulfonyl)quinoline



C17 H13 F2 N O3 S2; Mol wt: 381.4217

ACTION – Selective cyclooxygenase type 2 (COX-2) inhibitor, as demonstrated *in vitro* by IC₅₀ values of < 0.20 and < 40 μM against COX-2 and COX-1, respectively. Potentially useful for the treatment of inflammatory conditions such as myositis, synovitis, arthritis, gout, back pain, dental pain, sports injuries, sprains, strains, headache, tendonitis, ankylosing spondylitis and bursitis. Other exemplified quinoline derivatives are:



Compound	R1	R2	Formula
317139	Cl	H	C ₁₇ H ₁₄ ClNO ₃ S ₂
317140	Cl	F	C ₁₇ H ₁₃ ClFNO ₃ S ₂
317141	H	Br	C ₁₇ H ₁₄ BrNO ₃ S ₂
317142	Cl	Cl	C ₁₇ H ₁₃ Cl ₂ NO ₃ S ₂

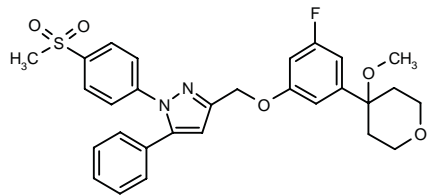
SOURCE – Roche.

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317304

3-[3-Fluoro-5-(4-methoxytetrahydro-2H-pyran-4-yl)phenoxy-methyl]-1-[4-(methylsulfonyl)phenyl]-5-phenyl-1H-pyrazole



C29 H29 F N2 O5 S; Mol wt: 536.6211

ACTION – Dual inhibitor of cyclooxygenase type 2 (COX-2) and 5-lipoxygenase (IC₅₀ = 50 and 3 nM, respectively) with high selectivity over COX-1 (IC₅₀ > 10 μM). It showed antiinflammatory activity in a model of ear edema induced by arachidonic acid in rats after both i.v. (0.01-0.1 μg/kg) and oral (0.1-5 mg/kg) administration.

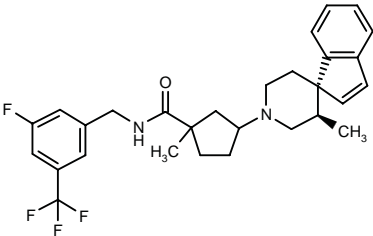
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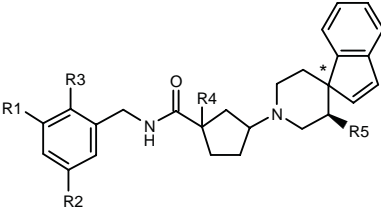
317449

N-[3-Fluoro-5-(trifluoromethyl)benzyl]-1-methyl-3-[(1*R*,3'*R*)-3'-methyl-1*H*-spiro[indene-1,4'-piperidin]-1'-yl]-cyclopentanecarboxamide

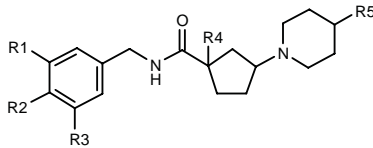


C29 H32 F4 N2 O; Mol wt: 500.5768

ACTION – A modulator of chemokine receptors, particularly CCR2. As such, this compound is expected to be useful for the treatment of inflammatory and immune disorders, including rheumatoid arthritis. Other specifically claimed compounds are:



Compound	R1	R2	R3	R4	R5	*Isomer	Formula
317450	H	H	OMe	Me	Me	R	C ₂₉ H ₃₆ N ₂ O ₂
317451	CF3	CF3	H	C6H13	Me	R	C ₃₈ H ₄₂ F ₆ N ₂ O
317454	CF3	CF3	H	H	H		C ₂₈ H ₂₈ F ₆ N ₂ O



Compound	R1	R2	R3	R4	R5	Formula
317452	F	F	H	i-Pr	4-F-Ph	C ₂₇ H ₃₃ F ₃ N ₂ O
317453	CF3	H	F	cyclopropyl	Ph	C ₂₈ H ₃₂ F ₄ N ₂ O
317455	CF3	H	CF3	i-Pr	Me	C ₂₄ H ₃₂ F ₆ N ₂ O
317456	CF3	H	F	2-(MeSO2NHCO)-cyclopropyl	4-F-Ph	C ₃₀ H ₃₄ F ₃ N ₃ O ₄ S
317457	CF3	H	CF3	CH2OAc	4-F-Ph	C ₂₉ H ₃₁ F ₇ N ₂ O ₃

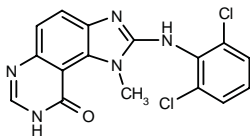
SOURCE – Merck & Co.

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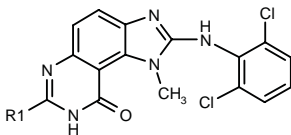
317508

2-(2,6-Dichlorophenylamino)-1-methyl-8,9-dihydro-1*H*-imidazo[4,5-*f*]quinazolin-9-one



C16 H11 Cl2 N5 O; Mol wt: 360.2029

ACTION – An inhibitor of protein tyrosine kinases, particularly Src and platelet-derived growth factor (PDGF) receptor kinases. Potentially useful for the treatment of autoimmune diseases such as rheumatoid arthritis, multiple sclerosis, Guillain-Barré syndrome, Crohn’s disease, ulcerative colitis, psoriasis, transplant rejection, systemic lupus erythematosus, type 1 diabetes and asthma, and also cancer and stroke. Other specifically claimed nitrogen-containing tricyclic compounds include the following:



Compound	R1	Formula
317509	2-(3-NO ₂ -Ph)-4-thiazolyl	C ₂₅ H ₁₅ Cl ₂ N ₇ O ₃ S
317510	C(Me)=CH ₂	C ₁₉ H ₁₅ Cl ₂ N ₅ O
317511	3-(1-Piz)-1-cyclopenten-1-yl	C ₂₅ H ₂₅ Cl ₂ N ₇ O
317512	3-[4-(t-BuOCO)-1-Piz]-1-cyclopenten-1-yl	C ₃₀ H ₃₃ Cl ₂ N ₇ O ₃
317513	2-[1-(PhCH ₂ OCO)-3-PipCH ₂]-4-thiazolyl	C ₃₃ H ₂₉ Cl ₂ N ₇ O ₃ S
317514	3-(NH ₂ CH ₂)-PhCH=C(Me)	C ₂₆ H ₂₂ Cl ₂ N ₆ O
317515	7-azabicyclo[2.2.1]hepta-2,5-dien-2-yl	C ₂₂ H ₁₆ Cl ₂ N ₆ O
317516	4-(1-Piz-SO ₂)-Ph	C ₂₆ H ₂₃ Cl ₂ N ₇ O ₃ S

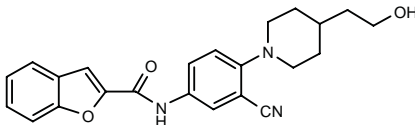
SOURCE – Boehringer Ingelheim.

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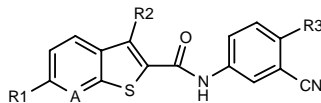
317616

N-[3-Cyano-4-[4-(2-hydroxyethyl)piperidin-1-yl]phenyl]-1-benzofuran-2-carboxamide

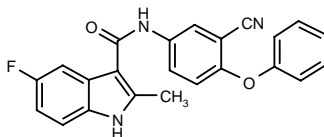


C23 H23 N3 O3; Mol wt: 389.4527

ACTION – Agent with the ability to inhibit activated lymphocyte proliferation, and thus potentially useful for the treatment of autoimmune diseases. The compound inhibited PMA-stimulated proliferation of rat lymphocytes with an IC₅₀ of 0.23 μM. It is reported to be active *in vivo* in mouse models of collagen-induced arthritis, lupus nephritis and ovalbumin-induced ear edema, and also in a rat model of experimental autoimmune encephalomyelitis. Other exemplified fused bicyclic amide compounds are:



Compound	R1	R2	R3	A	Formula
317618	H	H	4-(CH ₂ CH ₂ OH)-1-Piz	CH	C ₂₂ H ₂₂ N ₄ O ₂ S
317619	i-Pr	OH	t-BuCH ₂ O	N	C ₂₃ H ₂₅ N ₃ O ₃ S



317617: C23 H16 F N3 O2

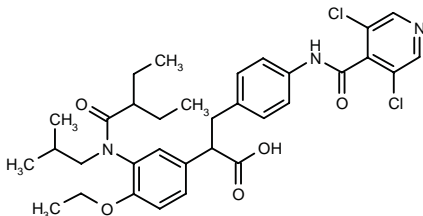
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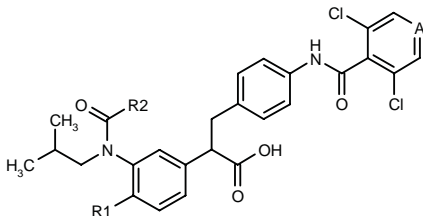
317679

3-[4-(3,5-Dichloropyridin-4-ylcarboxamido)phenyl]-2-[4-ethoxy-3-(2-ethyl-*N*-isobutylbutyramido)phenyl]propionic acid



C33 H39 Cl2 N3 O5; Mol wt: 628.5931

ACTION – VLA-4 antagonist shown to inhibit the adhesion of VLA-4-expressing HL-60 cells to VCAM-1-transfected CHO cells *in vitro* with an IC₅₀ of 0.11 nM. Potentially useful for the treatment of autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and Sjögren’s syndrome, allergic diseases including asthma, atopic dermatitis and rhinitis, inflammatory disorders such as inflammatory bowel disease, nephritis, hepatitis and CNS inflammatory conditions, and also cardiovascular disorders, arterio-sclerosis, diabetes, cancer and transplant rejection. Other exemplified 2,3-diphenylpropionic acid derivatives are:



Compound	R1	R2	A	Formula
317680	OPr	CH(Et)2	CH	C ₃₅ H ₄₂ Cl ₂ N ₂ O ₅
317681	OPr	CH(Et)2	N	C ₃₄ H ₄₁ Cl ₂ N ₃ O ₅
317682	Et	t-Bu	N	C ₃₂ H ₃₇ Cl ₂ N ₃ O ₄

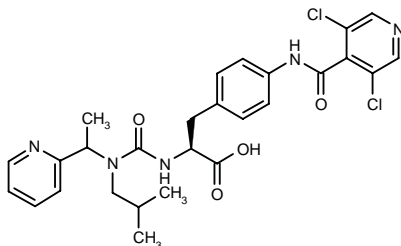
SOURCE – Kaken.

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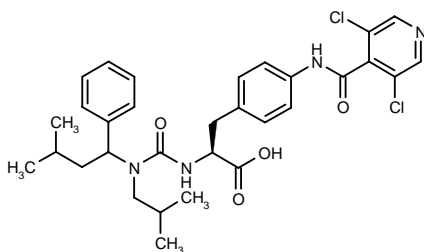
317684

4-(3,5-Dichloropyridin-4-ylcarboxamido)-*N*-[*N*-isobutyl-*N*-[1-(2-pyridyl)ethyl]carbonyl]-*L*-phenylalanine



C27 H29 Cl2 N5 O4; Mol wt: 558.4631

ACTION – VLA-4 antagonist shown to inhibit the adhesion of VLA-4-expressing HL-60 cells to VCAM-1-transfected CHO cells *in vitro* with an IC_{50} of 0.014 nM. Potentially useful for the treatment of autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and Sjögren's syndrome, allergic diseases including asthma, atopic dermatitis and rhinitis, inflammatory disorders such as inflammatory bowel disease, nephritis, hepatitis and CNS inflammatory conditions, and also cardiovascular disorders, arteriosclerosis, diabetes, cancer and transplant rejection. Another exemplified 2,3-diphenylpropionic acid derivative is:



317685: C31 H36 Cl2 N4 O4

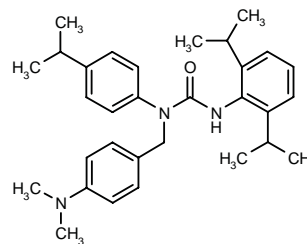
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317809

*N*¹-(2,6-Diisopropylphenyl)-*N*³-[4-(dimethylamino)benzyl]-*N*³-(4-isopropylphenyl)urea



C31 H41 N3 O; Mol wt: 471.6849

ACTION – A representative compound from a series of *N*¹,*N*³-diphenylurea derivatives that acts as a complement C5a antagonist, giving an IC_{50} value of 100 nM against C5a receptors expressed in U-937 cells. Using human neutrophils, it was shown to inhibit the C5a-stimulated increase in intracellular Ca^{2+} levels and neutrophil migration with IC_{50} values of 5 and 100 nM, respectively, suggesting antagonist activity. No agonist activity was observed at concentrations up to 10 μ M. Potentially useful for the treatment of autoimmune and allergic diseases such as rheumatism, systemic lupus erythematosus, sepsis, adult respiratory distress syndrome, chronic obstructive pulmonary disease and asthma, as well as other C5a-mediated disorders.

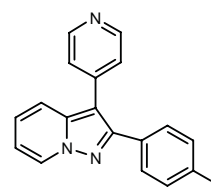
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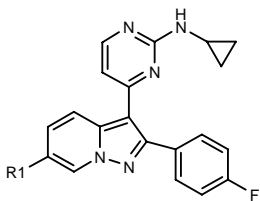
317886

2-(4-Fluorophenyl)-3-(4-pyridyl)pyrazolo[1,5-*a*]pyridine



C18 H12 F N3; Mol wt: 289.3118

ACTION – An inhibitor of p38 protein kinase (IC_{50} = 0.5 μ M) that was also shown to inhibit the lipopolysaccharide-stimulated production of TNF- α both *in vitro* in human peripheral blood mononuclear cells and *in vivo* following s.c. administration to mice at 30 mg/kg. In addition, the compound displayed low cytotoxicity when tested against human foreskin fibroblasts. Potentially useful for the treatment of inflammatory and autoimmune diseases. Other exemplified fused pyrazole derivatives are:



Compound	R1	Formula
317887	CN	C ₂₁ H ₁₅ FN ₆
317888	CONH2	C ₂₁ H ₁₇ FN ₆ O

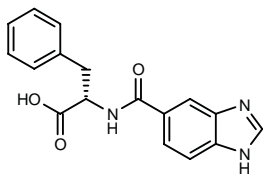
SOURCE – GlaxoSmithKline.

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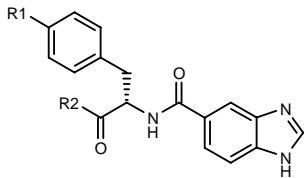
317895

N-(1*H*-Benzimidazol-5-ylcarbonyl)-L-phenylalanine



C17 H15 N3 O3; Mol wt: 309.3235

ACTION – Agent with the ability to inhibit neutrophil activity, adhesion and/or migration to endothelial cells, potentially useful for the treatment of inflammatory conditions including chronic inflammatory lung disease, ischemia–reperfusion injury, arthritis, inflammatory bowel disease, hepatitis, pancreatitis, allergy, gout, radiation-induced ulcer, fibrosis and migraine, inflammatory skin disease and cardiovascular and vascular diseases. Other compounds within this series are:



Compound	R1	R2	Formula
317896	H	ONa	C ₁₇ H ₁₄ N ₃ NaO ₃
317897	OAc	OH	C ₁₉ H ₁₇ N ₃ O ₅

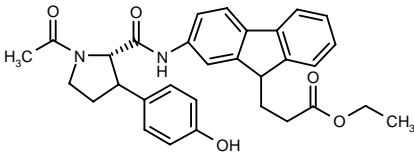
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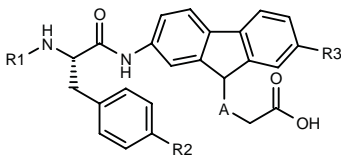
318046

3-[2-[1-Acetyl-3-(4-hydroxyphenyl)-L-prolylamino]-9*H*-fluoren-9-yl]propionic acid ethyl ester

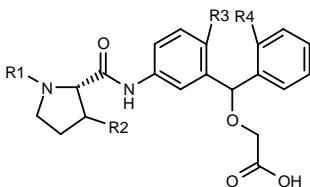


C31 H32 N2 O5; Mol wt: 512.6028

ACTION – Agent with affinity for integrin α_4 receptors and thus able to inhibit the interaction between α_4 integrin and MAdCAM and/or VCAM ligands. Potentially useful for the treatment of rheumatoid arthritis, asthma, psoriasis, multiple sclerosis, inflammatory bowel disease including ulcerative colitis and Crohn’s disease, celiac disease, nontropical sprue, transplant rejection, pancreatitis, type 1 diabetes, mastitis, cholecystitis, pericholangitis, chronic sinusitis, chronic bronchitis, pneumonitis, collagen disease, eczema and systemic lupus erythematosus. Other specifically claimed compounds are:



Compound	R1	R2	R3	A	Formula
318047	H	H	H	O	C ₂₄ H ₂₂ N ₂ O ₄
318048	H	H	H	CH2	C ₂₅ H ₂₄ N ₂ O ₃
318049	Ac	OH	H	CH2	C ₂₇ H ₂₆ N ₂ O ₅
318050	Ac	OH	2-Cl-Ph	CH2	C ₃₃ H ₂₉ ClN ₂ O ₅



Compound	R1	R2	R3	R4	Formula
318051	H	H	bond		C ₂₀ H ₂₀ N ₂ O ₄
318052	Ac	4-OH-Ph	H	H	C ₂₈ H ₂₈ N ₂ O ₆
318053	Ac	4-OH-Ph	-(CH2)2-		C ₃₀ H ₃₀ N ₂ O ₆

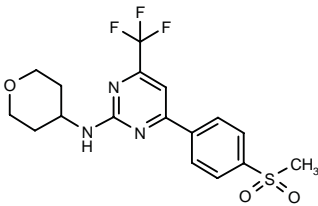
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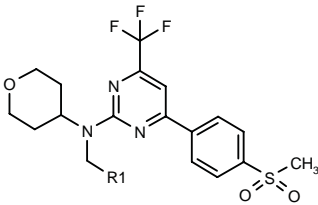
318137

4-[4-(Methylsulfonyl)phenyl]-N-(tetrahydropyran-4-yl)-6-(trifluoromethyl)pyrimidin-2-amine



C17 H18 F3 N3 O3 S; Mol wt: 401.4072

ACTION – A selective cyclooxygenase type 2 (COX-2) inhibitor with an IC₅₀ of 18 nM and > 5,000-fold selectivity over COX-1. Potentially useful for the treatment of acute and chronic pain, fever and inflammation. Other specifically claimed substituted pyrimidines are:



Compound	R1	Formula
318138	H	C ₁₈ H ₂₀ F ₃ N ₃ O ₃ S
318140	Me	C ₁₉ H ₂₂ F ₃ N ₃ O ₃ S

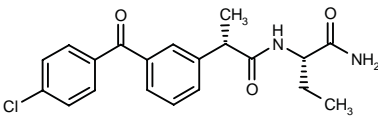
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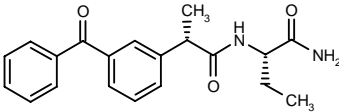
318154

2(S)-[2(S)-[3-(4-Chlorobenzoyl)phenyl]propionamido]-butyramide



C20 H21 Cl N2 O3; Mol wt: 372.8499

ACTION – Ketoprofen amide derivative with selective cyclooxygenase type 2 (COX-2)-inhibitory activity (IC₅₀ = 0.016 and < 0.01 μM in microsomal and cellular assays, respectively, vs. respective IC₅₀ values against COX-1 of 6.9 and 8.5 μM). Compound exhibited a good pharmacokinetic profile in rats, with a half-life of 3.9 h and high oral bioavailability (74%). In a model of Freund’s complete adjuvant-induced hind paw inflammation in rats, compound exhibited analgesic activity with an ED₅₀ value of 1.8 mg/kg. Another related compound is:



318152: C20 H22 N2 O3

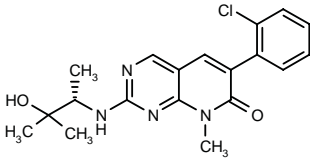
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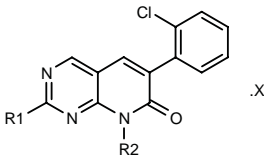
318157

6-(2-Chlorophenyl)-2-[2-hydroxy-1(S),2-dimethylpropyl-amino]-8-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one



C19 H21 Cl N4 O2; Mol wt: 372.8539

ACTION – An inhibitor of p38 kinase (IC₅₀ = 0.3 nM), potentially useful for the treatment of p38-mediated disorders including arthritis, Crohn’s disease, Alzheimer’s disease, irritable bowel syndrome, adult respiratory distress syndrome and chronic obstructive pulmonary disease. Other exemplified 7-oxopyridopyrimidines are:



Compound	R1	R2	X	Formula
318158	SO2Me	Me		C ₁₉ H ₁₂ ClN ₃ O ₃ S
318159	1-Me-4-Pip-CH2NH	H		C ₂₀ H ₂₂ ClN ₅ O
318160	1-[N(Me)2COCH2]-4-Pip-CH2NH	H	2HCl	C ₂₃ H ₂₇ ClN ₆ O ₂ ·2HCl
318161	NHC(Me)2CH2OH	Me		C ₁₈ H ₁₉ ClN ₄ O ₂
318163	NHC(CH2OH)2Me	Me		C ₁₈ H ₁₉ ClN ₄ O ₃
318164	NHC(CH2OH)2Et	Me		C ₁₉ H ₂₁ ClN ₄ O ₃
318165	(S)-NHCH(<i>i</i> -Pr)CH2OH	Me		C ₁₉ H ₂₁ ClN ₄ O ₂
318167	(S)-NHCH(Et)CH2OH	Me		C ₁₈ H ₁₉ ClN ₄ O ₂
318168	NHCH(CH2OH)2	Me		C ₁₇ H ₁₇ ClN ₄ O ₃

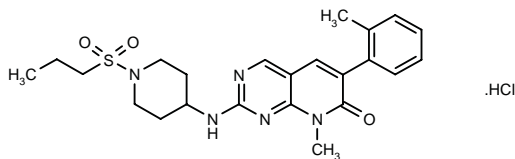
SOURCE – Roche.

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1. Arzeno, H.B. et al. (F. Hoffmann-La Roche AG) *7-Oxo pyridopyrimidines*. WO 0218379.

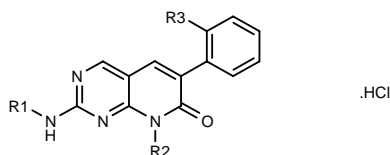
318170

8-Methyl-6-(2-methylphenyl)-2-[1-(propylsulfonyl)piperidin-4-ylamino]pyrido[2,3-*d*]pyrimidin-7(8*H*)-one hydrochloride



C23 H29 N5 O3 S . HCl; Mol wt: 492.0410

ACTION – An inhibitor of p38 kinase ($IC_{50} = 0.3$ nM), potentially useful for the treatment of p38-mediated disorders including arthritis, Crohn's disease, Alzheimer's disease, irritable bowel syndrome, adult respiratory distress syndrome and chronic obstructive pulmonary disease. Other exemplified 7-oxopyridopyrimidines are:



Compound	R1	R2	R3	Formula
318171	1-(CONH2)-4-Pip	Me	Cl	C ₂₀ H ₂₁ ClN ₆ O ₂ .HCl
318172	trans-4-NH2-cyclohexyl	Me	Cl	C ₂₀ H ₂₂ ClN ₅ O ₂ .HCl
318173	trans-4-OH-cyclohexyl	CH2Ph	Cl	C ₂₆ H ₂₅ ClN ₄ O ₂ .HCl
318174	trans-OH-cyclohexyl	CH2CN	Cl	C ₂₁ H ₂₀ ClN ₅ O ₂ .HCl
318175	4-THP	Me	Cl	C ₁₉ H ₁₉ ClN ₄ O ₂ .HCl
318176	1-(CF3CH2SO2)-4-Pip	Me	Me	C ₂₂ H ₂₄ F ₃ N ₅ O ₃ S.HCl
318177	4-THP	Et	Cl	C ₂₀ H ₂₁ ClN ₄ O ₂ .HCl

SOURCE – Roche.

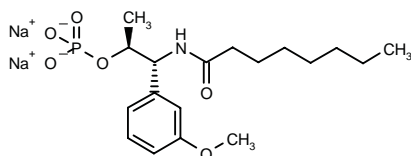
REFERENCES

1. Chen, J.J. et al. (F. Hoffmann-La Roche AG) 7-Oxo pyridopyrimidines as inhibitors of a cellular proliferation. WO 0218380.

318518

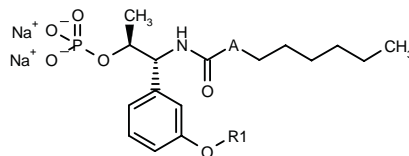
Phosphoric acid 2(*R*)-(3-methoxyphenyl)-1(*S*)-methyl-2-(octanamido)ethyl monoester disodium salt

N-[1(*R*)-(3-Methoxyphenyl)-2(*S*)-phosphonoxopropyl]-octanamide disodium salt



C18 H28 N Na2 O6 P; Mol wt: 431.3742

ACTION – TNF- α production inhibitor ($ID_{50} = 0.03$ mg/kg i.v. in rats) proven to protect mice from death induced by lipopolysaccharide (LPS; MED = 0.3 mg/kg i.v.) and from hepatitis induced by (+)-galactosamine + LPS (MED = 0.3 mg/kg i.v.). Potentially useful as an antiarthritic agent. Other related compounds are:



Compound	R1	A	Formula
318519	i-Pr	CH2	C ₂₀ H ₃₂ NNa ₂ O ₆ P
318520	Me	O	C ₁₇ H ₂₆ NNa ₂ O ₇ P

SOURCE – Ono.

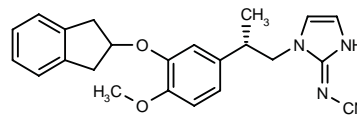
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1. Matsui, T. and Ohmawari, N. (Ono Pharmaceutical Co., Ltd.) Drugs containing phosphoric acid derivs. as the active ingredient. EP 1156054, WO 0050429.

2. Matsui, T. et al. Highly potent inhibitors of TNF- α production. Part 2: Identification of drug candidates. Bioorg Med Chem Lett 2002, 12(6): 907.

318597

(-)-1-[2(*S*)-[3-(2,3-Dihydro-1*H*-inden-2-yloxy)-4-methoxyphenyl]propyl]-2,3-dihydro-1*H*-imidazol-2-ylidene-cyanamide



C23 H24 N4 O2; Mol wt: 388.4686

ACTION – Potent and selective phosphodiesterase type 4 (PDE4) inhibitor ($IC_{50} = 57$ nM against recombinant PDE4 B from human mononuclear lymphocytes) with low affinity for rolipram binding sites ($K_i = 220$ nM) and low gastrointestinal side effects compared to the reference RP-73401. In the TPA-induced ear inflammation model in mice, topical application of compound at 1 mg/kg inhibited edema by 54%. Potentially useful as an antiinflammatory agent.

SOURCE – Janssen.

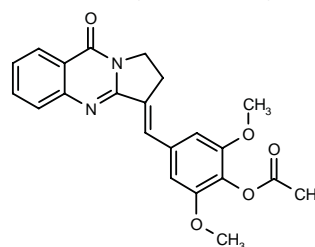
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1. Freyne, E.J.E. et al. (Janssen Pharmaceutica NV) PDE IV inhibiting 2-cyano-iminoimidazole derivs. WO 9814432.

2. Andrés, J.I. et al. Synthesis and biological evaluation of imidazol-2-one and 2-cyano-iminoimidazole derivatives: Novel series of PDE4 inhibitors. Bioorg Med Chem Lett 2002, 12(4): 653.

318815

Acetic acid 2,6-dimethoxy-4-(9-oxo-1,2,3,9-tetrahydropyrrolo[2,1-*b*]quinazolin-3-ylidenemethyl)phenyl ester



C22 H20 N2 O5; Mol wt: 392.4090

ACTION – Potent and selective cyclooxygenase type 2 (COX-2) inhibitor ($IC_{50} = 1.2 \mu M$ in human monocytes) with 5-10-fold selectivity over COX-1 ($IC_{50} > 10 \mu M$). It also inhibited human neutrophil 5-lipoxygenase ($IC_{50} = 0.6 \mu M$), as well as lipopolysaccharide-induced PGE_2 production in macrophages ($IC_{50} = 0.2 \mu M$). Compound exhibited strong efficacy in mouse models of acute inflammation. In the air pouch model, it significantly reduced zymosan-induced leukocyte infiltration ($ED_{50} = 12.8 \text{ nmol/pouch}$) and LTB_4 increase ($ED_{50} = 7.9 \text{ nmol/pouch}$), whereas it did not affect PGE_2 levels. In the carrageenan-induced paw edema model, it dose-dependently reduced swelling with an ED_{50} value of 27.2 mg/kg p.o. at 3 h after carrageenan administration; a slight reduction in PGE_2 levels was observed at the dose of 20 mg/kg p.o. In the third model, compound inhibited writhing induced by phenyl-*p*-benzoquinone with an ED_{50} value of 2.6 mg/kg p.o. No analgesic activity was seen in the hot-plate test in mice at the dose of 20 mg/kg p.o.

SOURCES – Universidad de Murcia, Murcia (ES); Universidad de Valencia, Valencia (ES).

REFERENCES

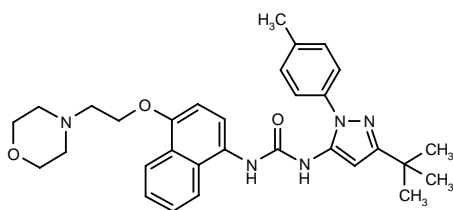
1. Molina, P. et al. *Inhibition of leukocyte functions by the alkaloid isaindigotone from Isatis indigotica and some new synthetic derivatives*. J Nat Prod 2001, 64(10): 1297.
2. Rioja, I. et al. *A pyrroloquinazoline derivative with anti-inflammatory and analgesic activity by dual inhibition of cyclo-oxygenase-2 and 5-lipoxygenase*. Eur J Pharmacol 2002, 434(3): 177.

BIRB-796*

292897

N-[3-*tert*-Butyl-1-(4-methylphenyl)-1-*H*-pyrazol-5-yl]-*N'*-[4-[2-(4-morpholinyl)ethoxy]naphthalen-1-yl]urea

BIRB-0796
BIRB-796 BS



C31 H37 N5 O3; Mol wt: 527.6653

ACTION – Oral antiinflammatory agent, an inhibitor of p38 MAP kinase able to inhibit the synthesis of $TNF-\alpha$ and other proinflammatory cytokines in mice, monkeys and man. It showed antiinflammatory activity in preclinical models of inflammation associated with neutrophil influx including peritonitis and arthritis. Compound is undergoing phase II clinical evaluation for the treatment of psoriasis, arthritis and ulcerative colitis. Results of phase I studies in healthy volunteers showed that compound given as single doses (1-600 mg) was generally well tolerated and no serious drug-related adverse events were observed. It showed a good pharmacokinetic profile, with a mean t_{max} of 0.75-2.25 h and a plasma half-life of 7.6-9.9 h. The pharmacodynamic effects of the compound, measured as *ex vivo* inhibition of lipopolysaccharide-induced $TNF-\alpha$ production and neutrophil activation, were related to plasma levels, although it was much more effective in inhibiting neutrophil activation than $TNF-\alpha$ production.

SOURCE – Boehringer Ingelheim.

REFERENCES

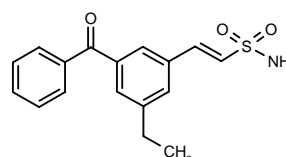
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2. Cirillo, P.F. et al. (Boehringer Ingelheim Pharmaceuticals Inc.) *Aromatic heterocyclic cpds. as antiinflammatory agents*. EP 1147104, US 6319921, WO 0043384.
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6. Gupta, A. et al. *Safety, pharmacokinetics, and pharmacodynamics of single doses of an oral p38 MAP kinase inhibitor (BIRB 796 BS) in healthy human males, a placebo-controlled, randomised study, double blinded at each dose level*. J Allergy Clin Immunol 2002, 109(1, Part 2): Abst 158.
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10. Pargellis, C. et al. *A novel series of p38 MAP kinase inhibitors: Development of a clinical candidate, BIRB0796*. Inflamm Res 2001, 50(Suppl. 3): Abst 01/01.
11. Pargellis, C. et al. *Inhibition of p38 MAP kinase by utilizing a novel allosteric binding site*. Nat Struct Biol 2002, 9(4): 268.
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*Identified compound **292897** Drug Data Rep 2001, 023(01): 0068.

LM-1669

318548

2-(3-Benzoyl-5-ethylphenyl)ethenesulfonamide



C17 H17 N O3 S; Mol wt: 315.3913

ACTION – Potent and selective cyclooxygenase type 2 (COX-2) inhibitor ($IC_{50} = 12$ and $0.20 \mu M$ in human whole blood assay and isolated monocytes, respectively) with moderate activity against the COX-1 enzyme ($IC_{50} = 100$ and $18 \mu M$, respectively). Potentially useful as an anti-inflammatory agent.

SOURCE – Menarini.

REFERENCES

1. Mauleón Casellas, D. et al. *Trisubstd. benzenes linked to amides, esters and carboxylic acids as new cyclooxygenase II inhibitors*. ES 2164564.

2. Palomer, A. et al. *Structure-based design of cyclooxygenase-2 selectivity into ketoprofen*. Bioorg Med Chem Lett 2002, 12(4): 533.

MAB M15

317268

Monoclonal antibody directed to murine CD30L

ACTION – A monoclonal antibody that blocks the interaction between CD30 and CD30L and is thus potentially useful for the treatment of autoimmune and chronic inflammatory diseases such as rheumatoid arthritis. In a model of collagen-induced arthritis in mice, daily injections of M15 significantly improved mean clinical scores, resulting in a lower disease incidence and a decrease in the number of animals with severe disease. The antibody M15 was also effective in ameliorating chronic experimental autoimmune encephalomyelitis in mice and delayed renal failure in a murine model of systemic lupus erythematosus.

SOURCE – Immunex.

REFERENCES

1. Mohler, K.M. et al. (Immunex Corp.) *Methods for treating autoimmune and chronic inflammatory conditions using antagonists of CD30 or CD30L*. WO 0211767.

TNV-148

317218

Monoclonal antibody to human tumor necrosis factor (TNF)

ACTION – Monoclonal antibody specific for human TNF, shown to inhibit TNF-induced cell adhesion molecules and TNF binding to recombinant receptors. TNV-148 was active in arthritic mice when administered at doses of 1-10 mg/kg i.p.

SOURCE – Centocor.

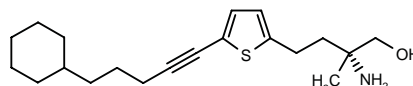
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1. Giles-Komar, J. et al. (Centocor Inc.) *Anti-TNF antibodies, compsns., methods and uses*. WO 0212502.

IMMUNOMODULATING AGENTS

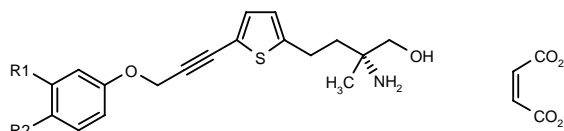
316997

2(*R*)-Amino-4-[5-(5-cyclohexyl-1-pentynyl)thien-2-yl]-2-methylbutan-1-ol

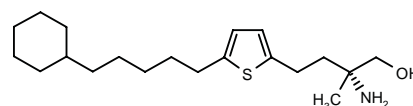


C20 H31 N O S; Mol wt: 333.5369

ACTION – Immunosuppressant with *in vivo* activity in a rat model of graft-vs.-host reaction ($ID_{50} = 0.0843$ mg/kg p.o.). Compound also inhibited adjuvant-induced arthritis in rats with an ID_{50} value of 0.0897 mg/kg p.o. Potentially useful for the treatment of a broad range of immune and inflammatory disorders including systemic lupus erythematosus, arthritis, Crohn's disease, ulcerative colitis, psoriasis, sarcoidosis, asthma, myocarditis, pulmonary hypertension, nephritis, dermatitis, systemic sclerosis, diabetes, atherosclerosis, cirrhosis, transplant rejection, sepsis, etc. Other exemplified thiophene-containing amino alcohol compounds are:



Compound	R1	R2	Formula
316999	H	Me	C ₁₉ H ₂₃ NO ₂ S.C ₄ H ₄ O ₄
317001	OMe	OMe	C ₂₀ H ₂₅ NO ₄ S.C ₄ H ₄ O ₄
317002	OMe	H	C ₁₉ H ₂₃ NO ₃ S.C ₄ H ₄ O ₄
317003	Me	Me	C ₂₀ H ₂₅ NO ₂ S.C ₄ H ₄ O ₄



317000: C20 H35 N O S

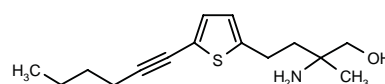
SOURCE – Sankyo.

REFERENCES

1. Nishi, T. et al. (Sankyo Co., Ltd.) *Amino alcohol derivs*. WO 0206268.

317810

2-Amino-4-[5-(1-hexynyl)thien-2-yl]-2-methylbutan-1-ol



C15 H23 N O S; Mol wt: 265.4187

ACTION – Immunosuppressant reported to have low toxicity. Other exemplified thienyl-containing amino-alcohols include the following:

SOURCE – Menarini.

REFERENCES

1. Mauleón Casellas, D. et al. *Trisubstd. benzenes linked to amides, esters and carboxylic acids as new cyclooxygenase II inhibitors*. ES 2164564.

2. Palomer, A. et al. *Structure-based design of cyclooxygenase-2 selectivity into ketoprofen*. Bioorg Med Chem Lett 2002, 12(4): 533.

MAB M15

317268

Monoclonal antibody directed to murine CD30L

ACTION – A monoclonal antibody that blocks the interaction between CD30 and CD30L and is thus potentially useful for the treatment of autoimmune and chronic inflammatory diseases such as rheumatoid arthritis. In a model of collagen-induced arthritis in mice, daily injections of M15 significantly improved mean clinical scores, resulting in a lower disease incidence and a decrease in the number of animals with severe disease. The antibody M15 was also effective in ameliorating chronic experimental autoimmune encephalomyelitis in mice and delayed renal failure in a murine model of systemic lupus erythematosus.

SOURCE – Immunex.

REFERENCES

1. Mohler, K.M. et al. (Immunex Corp.) *Methods for treating autoimmune and chronic inflammatory conditions using antagonists of CD30 or CD30L*. WO 0211767.

TNV-148

317218

Monoclonal antibody to human tumor necrosis factor (TNF)

ACTION – Monoclonal antibody specific for human TNF, shown to inhibit TNF-induced cell adhesion molecules and TNF binding to recombinant receptors. TNV-148 was active in arthritic mice when administered at doses of 1-10 mg/kg i.p.

SOURCE – Centocor.

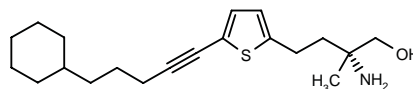
REFERENCES

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IMMUNOMODULATING AGENTS

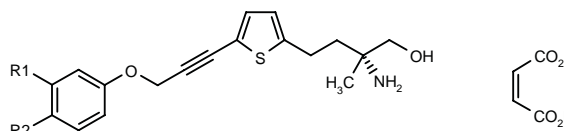
316997

2(*R*)-Amino-4-[5-(5-cyclohexyl-1-pentynyl)thien-2-yl]-2-methylbutan-1-ol

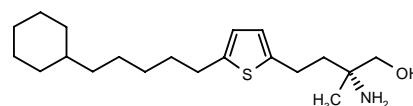


C20 H31 N O S; Mol wt: 333.5369

ACTION – Immunosuppressant with *in vivo* activity in a rat model of graft-vs.-host reaction ($ID_{50} = 0.0843$ mg/kg p.o.). Compound also inhibited adjuvant-induced arthritis in rats with an ID_{50} value of 0.0897 mg/kg p.o. Potentially useful for the treatment of a broad range of immune and inflammatory disorders including systemic lupus erythematosus, arthritis, Crohn's disease, ulcerative colitis, psoriasis, sarcoidosis, asthma, myocarditis, pulmonary hypertension, nephritis, dermatitis, systemic sclerosis, diabetes, atherosclerosis, cirrhosis, transplant rejection, sepsis, etc. Other exemplified thiophene-containing amino alcohol compounds are:



Compound	R1	R2	Formula
316999	H	Me	C ₁₉ H ₂₃ NO ₂ S.C ₄ H ₄ O ₄
317001	OMe	OMe	C ₂₀ H ₂₅ NO ₄ S.C ₄ H ₄ O ₄
317002	OMe	H	C ₁₉ H ₂₃ NO ₃ S.C ₄ H ₄ O ₄
317003	Me	Me	C ₂₀ H ₂₅ NO ₂ S.C ₄ H ₄ O ₄



317000: C20 H35 N O S

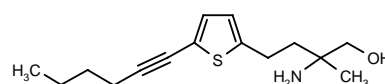
SOURCE – Sankyo.

REFERENCES

1. Nishi, T. et al. (Sankyo Co., Ltd.) *Amino alcohol derivs*. WO 0206268.

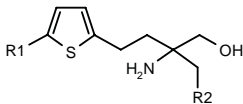
317810

2-Amino-4-[5-(1-hexynyl)thien-2-yl]-2-methylbutan-1-ol



C15 H23 N O S; Mol wt: 265.4187

ACTION – Immunosuppressant reported to have low toxicity. Other exemplified thienyl-containing amino-alcohols include the following:



Compound	R1	R2	Formula
317811	C6H13-ethynyl	H	C ₁₇ H ₂₇ NOS
317812	C6H13	H	C ₁₅ H ₂₇ NOS
317813	C8H17	H	C ₁₇ H ₃₁ NOS
317814	COC7H15	H	C ₁₇ H ₂₉ NO ₂ S
317815	Bu-ethynyl	Me	C ₁₆ H ₂₅ NOS
317816	C7H15-ethynyl	Me	C ₁₉ H ₃₁ NOS
317817	COC5H11	Me	C ₁₆ H ₂₇ NO ₂ S
317818	COC7H15	Me	C ₁₈ H ₃₁ NO ₂ S

SOURCE – Sankyo.

REFERENCES

1. Nishi, T. and Takemoto, T. (Sankyo Co., Ltd.) *Aminoalcohols*. JP 2002053575.

ANTI-TIRC7 MAb

318678

Anti-T-cell immune response cDNA 7 (TIRC7) monoclonal antibody

ACTION – Monoclonal antibody against the T-cell membrane molecule TIRC7, proven to prevent T-cell activation *in vitro* and *in vivo*, as well as acute allograft rejection in mice with fully MHC-mismatched cardiac transplant. Mice treated with the antibody just before and 5 days after transplantation showed markedly increased graft survival time (from 8 days in untreated animals to 52 days) and some animals showed long-term survival of > 120 days. In addition, the antibody significantly reduced mononuclear cell infiltration and expression of CD25 and CD28 in splenocytes; it also increased CTLA4 expression compared to controls. Potentially useful for the prevention of transplant rejection and for the treatment of other immune-related diseases.

SOURCES – GenPat77; Humboldt-Universität zu Berlin, Berlin (DE).

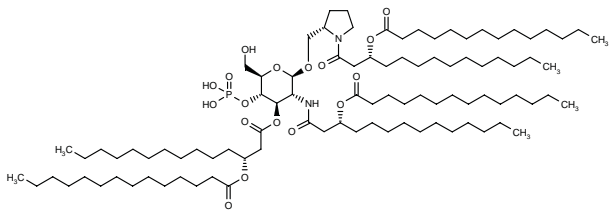
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1. Kumamoto, Y. et al. *Induction therapy with monoclonal antibodies targeting the novel molecule, TIRC7, delays the onset of acute cardiac allograft rejection in mice*. Am J Transplant 2002, 2(Suppl. 3): Abst 982.

RC-553

317122

2-Deoxy-2-[3(*R*)-(tetradecanoyloxy)tetradecanamido]-3-*O*-[3(*R*)-(tetradecanoyloxy)tetradecanoyl]-1-*O*-[1-[3(*R*)-(tetradecanoyloxy)tetradecanoyl]pyrrolidin-2(*S*)-ylmethyl]-β-D-glucopyranose 4-*O*-phosphate



C95 H179 N2 O17 P; Mol wt: 1652.4300

ACTION – An acylated glucosamine immunoeffector with potential as an adjuvant in vaccination therapies. Compound increased serum IgG titers in response to hepatitis B and influenza vaccines, as demonstrated in BALB/c mice.

SOURCE – Corixa.

REFERENCES

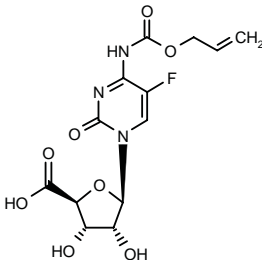
1. Johnson, D.A. et al. (Corixa Corp.) *New immunoeffector cpds*. WO 0212258.

ONCOLYTIC DRUGS

ANTIMETABOLITES

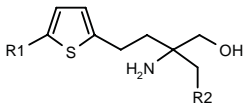
317419

1-[4-(Allyloxycarbonylamino)-5-fluoro-2-oxo-1,2-dihydro-pyrimidin-1-yl]-1-deoxy-β-D-ribofuranuronic acid



C13 H14 F N3 O8; Mol wt: 359.2646

ACTION – Antineoplastic agent, a derivative of 5-fluorocytosine with cytotoxic activity against a panel of human tumor cells including lung A549, ovarian SK-OV-3, colon HCT-15 and melanoma SK-MEL-2 cells (IC₅₀ = 0.08-0.04 μg/ml). It exhibited potent antitumor activity, superior to capecitabine, in a murine leukemia L1210 model and it exhibited low toxicity after acute (LD₅₀ = 650 mg/kg) and chronic (LD₅₀ = 22 mg/kg/day for 21 days) oral administration to mice.



Compound	R1	R2	Formula
317811	C6H13-ethynyl	H	C ₁₇ H ₂₇ NOS
317812	C6H13	H	C ₁₅ H ₂₇ NOS
317813	C8H17	H	C ₁₇ H ₃₁ NOS
317814	COC7H15	H	C ₁₇ H ₂₉ NO ₂ S
317815	Bu-ethynyl	Me	C ₁₆ H ₂₅ NOS
317816	C7H15-ethynyl	Me	C ₁₉ H ₃₁ NOS
317817	COC5H11	Me	C ₁₆ H ₂₇ NO ₂ S
317818	COC7H15	Me	C ₁₈ H ₃₁ NO ₂ S

SOURCE – Sankyo.

REFERENCES

1. Nishi, T. and Takemoto, T. (Sankyo Co., Ltd.) *Aminoalcohols*. JP 2002053575.

ANTI-TIRC7 MAb

318678

Anti-T-cell immune response cDNA 7 (TIRC7) monoclonal antibody

ACTION – Monoclonal antibody against the T-cell membrane molecule TIRC7, proven to prevent T-cell activation *in vitro* and *in vivo*, as well as acute allograft rejection in mice with fully MHC-mismatched cardiac transplant. Mice treated with the antibody just before and 5 days after transplantation showed markedly increased graft survival time (from 8 days in untreated animals to 52 days) and some animals showed long-term survival of > 120 days. In addition, the antibody significantly reduced mononuclear cell infiltration and expression of CD25 and CD28 in splenocytes; it also increased CTLA4 expression compared to controls. Potentially useful for the prevention of transplant rejection and for the treatment of other immune-related diseases.

SOURCES – GenPat77; Humboldt-Universität zu Berlin, Berlin (DE).

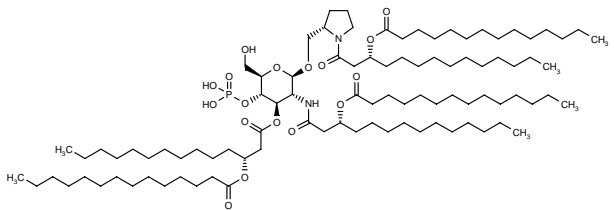
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RC-553

317122

2-Deoxy-2-[3(*R*)-(tetradecanoyloxy)tetradecanamido]-3-*O*-[3(*R*)-(tetradecanoyloxy)tetradecanoyl]-1-*O*-[1-[3(*R*)-(tetradecanoyloxy)tetradecanoyl]pyrrolidin-2(*S*)-ylmethyl]-β-D-glucopyranose 4-*O*-phosphate



C95 H179 N2 O17 P; Mol wt: 1652.4300

ACTION – An acylated glucosamine immunoeffector with potential as an adjuvant in vaccination therapies. Compound increased serum IgG titers in response to hepatitis B and influenza vaccines, as demonstrated in BALB/c mice.

SOURCE – Corixa.

REFERENCES

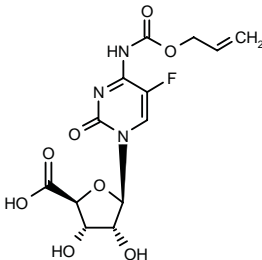
1. Johnson, D.A. et al. (Corixa Corp.) *New immunoeffector cpds*. WO 0212258.

ONCOLYTIC DRUGS

ANTIMETABOLITES

317419

1-[4-(Allyloxycarbonylamino)-5-fluoro-2-oxo-1,2-dihydro-pyrimidin-1-yl]-1-deoxy-β-D-ribofuranuronic acid



C13 H14 F N3 O8; Mol wt: 359.2646

ACTION – Antineoplastic agent, a derivative of 5-fluorocytosine with cytotoxic activity against a panel of human tumor cells including lung A549, ovarian SK-OV-3, colon HCT-15 and melanoma SK-MEL-2 cells (IC₅₀ = 0.08-0.04 μg/ml). It exhibited potent antitumor activity, superior to capecitabine, in a murine leukemia L1210 model and it exhibited low toxicity after acute (LD₅₀ = 650 mg/kg) and chronic (LD₅₀ = 22 mg/kg/day for 21 days) oral administration to mice.

SOURCE – Kolon Industries.

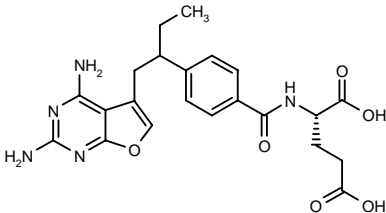
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2. Kim, K.-H. et al. *Synthesis and biological activity of the new 5-fluorocytosine derivatives, 5'-deoxy-N-alkyloxycarbonyl-5-fluorocytosine-5'-carboxylic acid.* Bioorg Med Chem Lett 2002, 12(3): 483.

318668

N-[4-[1(*R,S*)-(2,4-Diaminofuro[2,3-*d*]pyrimidin-5-yl-methyl)propyl]benzoyl]-L-glutamic acid



C22 H25 N5 O6; Mol wt: 455.4685

ACTION – Antineoplastic agent, an inhibitor of human dihydrofolate reductase (DHFR; IC₅₀ = 0.42 μM) with > 100-fold selectivity over *Trypanosoma gondii* and *Escherichia coli* DHFR (IC₅₀ = 2.1 and 1.1 μM, respectively); it was inactive up to 100 μM against human and *E. coli* thymidylate synthase. Compound showed cytotoxic activity against CCRF-CEM cells (IC₅₀ = 35.5 nM), as well as against an NCI panel of human cancer cells, with IC₅₀ values in the nanomolar range.

SOURCES – Duquesne University, Pittsburgh, PA (US); Roswell Park Cancer Institute, Buffalo, NY (US); Tufts University, Boston, MA (US).

REFERENCES

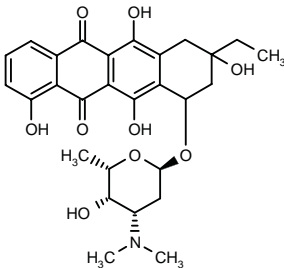
1. Gangjee, A. et al. *Synthesis of N-[4-[ethyl-2-(2,4-diaminofuro[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-L-glutamic acid as an antifolate.* J Med Chem 2002, 45(9): 1942.

ANTIBIOTICS AND ALKALOIDS

HU2-705E

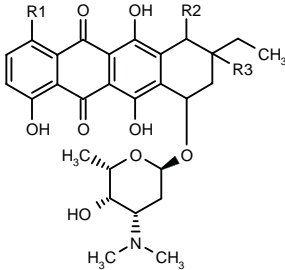
317749

3-Ethyl-3,5,10,12-tetrahydroxy-6,11-dioxo-1,2,3,4,6,11-hexahydrotetracen-1-yl 2,3,6-trideoxy-3-(dimethylamino)-α-L-galactopyranoside



C28 H33 N O9; Mol wt: 527.5667

ACTION – Antineoplastic agent isolated from cultures of *Streptomyces violaceus* HU2-705 (FERM P-17986), giving an IC₅₀ of 0.02 μg/ml against murine leukemia L1210 cells; it inhibited DNA and RNA biosynthesis with IC₅₀ values of 0.9 and 0.3 μg/ml, respectively. Other compounds from the same source are:



Compound	R1	R2	R3	Formula
HU2-705A [317750]	H	bond		C ₂₆ H ₃₁ NO ₈
HU2-705B [317752]	H	CO ₂ H	OH	C ₂₉ H ₃₃ NO ₁₁
HU2-705C [317753]	OH	CO ₂ H	OH	C ₂₉ H ₃₃ NO ₁₂

SOURCE – Mercian.

REFERENCES

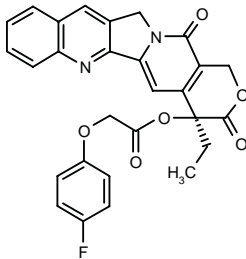
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DNA-INTERCALATING DRUGS

317542

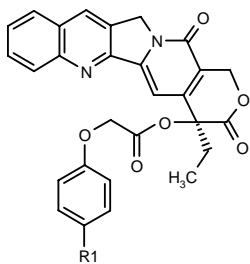
2-(4-Fluorophenoxy)acetic acid 4(*S*)-ethyl-3,14-dioxo-3,4,12,14-tetrahydro-1*H*-pyrano[3',4':6,7]indolizino[1,2-*b*]-quinolin-4-yl ester

20(*S*)-*O*-[2-(4-Fluorophenoxy)acetyl]camptothecin



C28 H21 F N2 O6; Mol wt: 500.4799

ACTION – Camptothecin ester derivative with antitumor activity, shown to be active against human colon carcinoma HCT 116 cells and human prostate adenocarcinoma PC-3 cells, completely inhibiting cell survival at 10 nM. In acute toxicity tests in mice, compound had a maximum tolerated dose at day 40 (MTD40) of > 150 mg/kg i.p. In addition, it was effective in prolonging the survival time of mice bearing mammary adenocarcinoma MTG-B xenografts, having superior efficacy when compared to paclitaxel. Other exemplified compounds are:



Compound	R1	Formula
317543	Br	C ₂₈ H ₂₁ BrN ₂ O ₆
317544	I	C ₂₈ H ₂₁ IN ₂ O ₆

SOURCE – California Pacific Medical Center Institute, San Francisco, CA (US).

REFERENCES

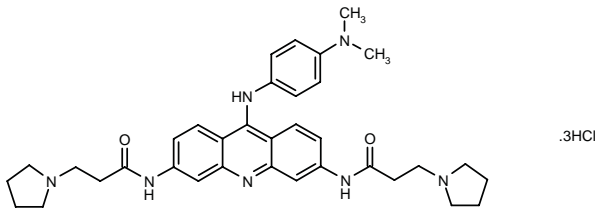
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ANTIMITOTIC DRUGS

BRACO-19

301620

N,N'-[9-[4-(Dimethylamino)phenylamino]acridin-3,6-diyl]-bis[3-(1-pyrrolidinyl)propionamide] trihydrochloride



C35 H43 N7 O2 . 3HCl; Mol wt: 703.1544

ACTION – Antineoplastic agent, a potent and selective small-molecule G-quadruplex-mediated inhibitor of telomerase (IC₅₀ = 60-115 nM) with low nonspecific cytotoxicity against a range of human tumor cell lines including epidermoid carcinoma A-431 cells and cisplatin-resistant and -sensitive ovarian cancer A2780, CH1 and SK-OV cells, with a mean IC₅₀ value of 10.6 μM. In addition, the exposure of human breast cancer 21NT cells (which possess relatively short telomeres) to nonacute cytotoxic concentrations of compound resulted in a strong reduction in cell growth after only 15 days, concomitant with a reduction in intracellular telomerase activity and onset of senescence. In mice bearing advanced-stage A-431 xenografts and previously treated with paclitaxel, compound provided a significant increase in antitumor activity compared with paclitaxel alone.

SOURCE – Institute of Cancer Research, London (GB).

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1. Neidle, S. et al. (Cancer Research Ventures Ltd.) *Therapeutic acridone and acridine cpds.* WO 0208193.

2. Gowan, S.M. et al. *A G-quadruplex-interactive potent small-molecule inhibitor of telomerase exhibiting in vitro and in vivo antitumor activity.* Mol Pharmacol 2002, 61(5): 1154.

3. Gowan, S.M. et al. *Preclinical antitumor properties of G-quadruplex interactive small molecule inhibitors of telomerase.* Proc Am Assoc Cancer Res 2001, 42: Abst 466.

4. Incles, C.M. et al. *Relationship between telomerase expression and sensitivity/resistance to novel cell signalling inhibitors.* Proc Am Assoc Cancer Res 2002, 43: Abst 1508.

5. Kelland, L.R. et al. *Antitumor and pharmacodynamic studies with small molecule inhibitors of telomerase.* Int J Mol Med 2001, 8(Suppl. 1): Abst 105.

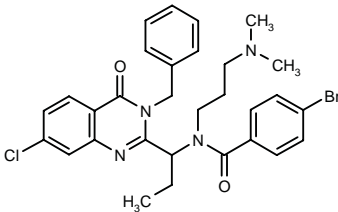
6. Li, J.-L. et al. *Inhibition of the Bloom's and Werner's syndrome helicases by G-quadruplex interacting ligands.* Biochemistry 2001, 40(50): 15194.

7. Read, M. et al. *Structure-based design of selective and potent G quadruplex-mediated telomerase inhibitors.* Proc Natl Acad Sci USA 2001, 98(9): 4844.

CK-0106023

317796

N-[1-(3-Benzyl-7-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)propyl]-4-bromo-*N*-[3-(dimethylamino)propyl]benzamide



C30 H32 Br Cl N4 O2; Mol wt: 595.9658

ACTION – Antimitotic agent, an inhibitor of kinesin spindle protein (KSP) shown to produce cell cycle arrest in mitosis in a wide range of human tumor cell lines. In nude mice bearing human ovarian carcinoma SK-OV-3 xenografts, compound inhibited tumor growth by 71% at half the maximum tolerated dose (MTD) and induced tumor regression at the MTD.

SOURCES – Cytokinetics; GlaxoSmithKline.

REFERENCES

1. Finer, J.T. et al. (Cytokinetics, Inc.) *Methods and compsns. utilizing quinazolinones.* WO 0198278.

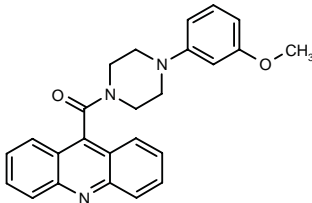
2. Lee, Y. et al. *Inhibitors of the mitotic kinesin KSP: Biochemical mechanism of action.* Proc Am Assoc Cancer Res 2002, 43: Abst 325.

3. Wood, K.W. et al. *Inhibitors of the mitotic kinesin KSP: Discovery and proof of principle anti-tumor activity.* Proc Am Assoc Cancer Res 2002, 43: Abst 3300.

D-82318

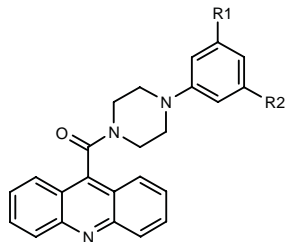
318241

1-(9-Acridinyl)-1-[4-(3-methoxyphenyl)piperazin-1-yl]-methanone



C25 H23 N3 O2; Mol wt: 397.4757

ACTION – Cytotoxic agent, an inhibitor of microtubule-associated protein (MAP)-rich tubulin polymerization ($IC_{50} = 0.80 \mu M$) with cytotoxic activity against a panel of human tumor cell lines including multidrug-resistant cell lines, with a mean IC_{50} of 70 nM. Compound interacted with the colchicine binding site and completely arrested cells in the G_2/M phase of the cell cycle. Other related compounds are:



Compound	R1	R2	Formula
D-81862 [316413]	OMe	OMe	C ₂₆ H ₂₅ N ₃ O ₃
D-82317 [318240]	Me	Me	C ₂₆ H ₂₅ N ₃ O

SOURCE – Zentaris.

REFERENCES

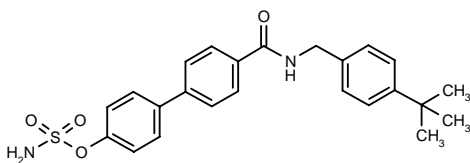
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2. Guenther, E.G. Sr. et al. *1-Phenyl-4-piperazinyl-carbonyl-substituted heterocyclic derivatives: A new class of highly potent cytotoxic compounds with inhibitory effects on the tubulin polymerization*. Proc Am Assoc Cancer Res 2002, 43: Abst 3654.

HORMONAL AGENTS

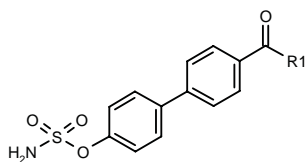
316988

Sulfamic acid 4'-[N-(4-*tert*-butylbenzyl)carbamoyl]biphenyl-4-yl ester



C24 H26 N2 O4 S; Mol wt: 438.5454

ACTION – Steroid sulfatase inhibitor ($IC_{50} = 2.5 \mu M$) for use in the treatment of estrone-dependent diseases including breast cancer, endometriosis, endometrial cancer and uterine myoma. Other exemplified biphenyl derivatives are:



Compound	R1	Formula
316990	4-t-Bu-PhCH2	C ₂₄ H ₂₅ NO ₄ S
316992	NHCH2CH2Ph	C ₂₁ H ₂₀ N ₂ O ₄ S
316993	NHOCH2Ph	C ₂₀ H ₁₈ N ₂ O ₅ S

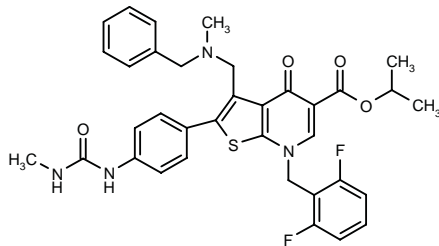
SOURCE – Nippon Organon.

REFERENCES

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317214

3-(*N*-Benzyl-*N*-methylaminomethyl)-7-(2,6-difluorobenzyl)-2-[4-(3-methylureido)phenyl]-4-oxo-4,7-dihydro-thieno[2,3-*b*]pyridine-5-carboxylic acid isopropyl ester



C35 H34 F2 N4 O4 S; Mol wt: 644.7396

ACTION – A representative compound from a series of thieno[2,3-*b*]pyridine-5-carboxylic acid derivatives that acts as a gonadotropin-releasing hormone (GnRH) antagonist. Compound inhibited [¹²⁵I]-leuporelin binding to GnRH receptors in rat pituitary membranes by 90% at 1 μM and was able to decrease blood testosterone levels at 30 mg/kg s.c. in monkeys. Potentially useful for the treatment of sex hormone-dependent disorders such as prostate, uterine, breast and pituitary cancer, prostatic hypertrophy, uterine myoma, endometriosis, precocious puberty, amenorrhea, Alzheimer's disease, polycystic ovary syndrome, contraception and sterility, as well as for modulating menstruation.

SOURCE – Takeda.

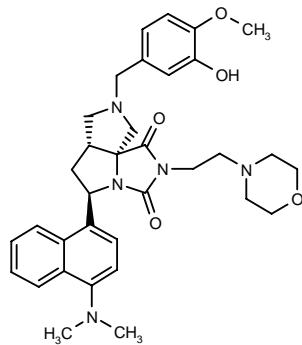
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AF-21276

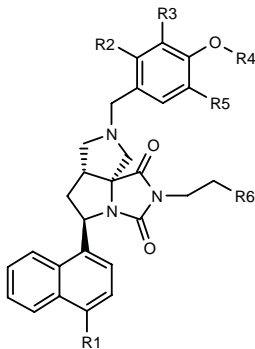
317021

(5*R*,6*aR*,9*aR*)-5-[4-(Dimethylamino)naphthalen-1-yl]-8-(3-hydroxy-4-methoxybenzyl)-2-[2-(4-morpholinyl)-ethyl]perhydropyrrolo[3',4':2,3]pyrrolo[1,2-*c*]imidazole-1,3-dione

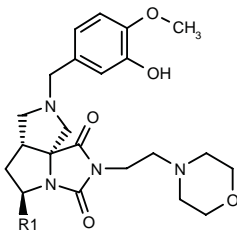


C34 H41 N5 O5; Mol wt: 599.7279

ACTION – Gonadotropin-releasing hormone (GnRH) antagonist (IC_{50} = 35 nM), potentially useful for the treatment of sex hormone-dependent conditions such as prostate, uterine and breast cancer, pituitary gonadotroph adenoma, endometriosis, polycystic ovary syndrome, uterine fibroids and precocious puberty, and also for use as a contraceptive. Other exemplified pyrrolidine derivatives are:



Compound	R1	R2	R3	R4	R5	R6	Formula
317023	N(Me)2	H	H	H	OEt	4-morpholinyl	C ₃₅ H ₄₃ N ₅ O ₅
317025	N(Me)2	Br	Br	H	OMe	4-morpholinyl	C ₃₄ H ₃₉ Br ₂ N ₅ O ₅
317026	N(Me)2	Br	H	Me	OH	4-morpholinyl	C ₃₄ H ₄₀ BrN ₅ O ₅
317028	OMe	H	H	Me	OH	4-morpholinyl	C ₃₃ H ₃₈ N ₄ O ₆
317030	N(Me)2	H	H	Me	OH	1-Piz	C ₃₄ H ₄₂ N ₆ O ₄
317031	N(Me)2	H	H	Me	OH	4-Pyr	C ₃₅ H ₃₇ N ₅ O ₄
317032	NH2	H	H	Me	OH	4-morpholinyl	C ₃₂ H ₃₇ N ₅ O ₅
317033	N(Me)2	H	H	Me	NHAc	4-morpholinyl	C ₃₆ H ₄₄ N ₆ O ₅



Compound	R1	Formula
317029	4-N(Me)2-Ph	C ₃₀ H ₃₉ N ₅ O ₅
317034	4-quinolyl	C ₃₁ H ₃₅ N ₅ O ₅
317035	3-quinolyl	C ₂₃ H ₂₇ N ₅ O ₃

SOURCE – GlaxoSmithKline.

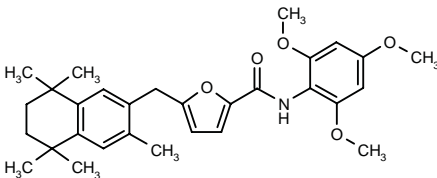
REFERENCES

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AXC-06728

318246

5-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydronaphthalen-2-ylmethyl)-N-(2,4,6-trimethoxyphenyl)furan-2-carboxamide



C30 H37 N O5; Mol wt: 491.6243

ACTION – Potent, orally active gonadotropin-releasing hormone (GnRH) receptor antagonist with low nanomolar binding affinity for human, rat and mouse receptors (K_i = 6.0, 3.8 and 2.2 nM, respectively) and functional antagonist activity *in vitro* (K_b = 25 nM in HEK-293 cells expressing the human GnRH receptor). Compound showed good oral bioavailability in male rats (40%); it dose-dependently suppressed GnRH-stimulated increases in luteinizing hormone (LH) in castrated male rats, as well as GnRH superagonist-stimulated increases in LH and testosterone in intact male rats. Complete sup-pression of circulating testosterone to castrate levels was obtained in intact rats after a single oral dose of 100 mg/kg and was maintained for over 12 h. Potentially useful for the treatment of hormone-dependent conditions such as prostate, breast and ovarian cancer.

SOURCE – Agouron (Pfizer).

REFERENCES

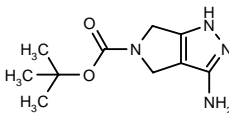
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2. Anderes, K. et al. *Biological characterization of a novel, bioavailable small molecule gonadotropin releasing hormone antagonist using clinically relevant biomarkers*. Proc Am Assoc Cancer Res 2002, 43: Abst 4790.

INHIBITORS OF SIGNAL
TRANSDUCTION PATHWAYS

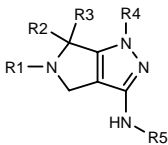
317298

3-Amino-1,4,5,6-tetrahydropyrrolo[3,4-*c*]pyrazole-5-carboxylic acid *tert*-butyl ester

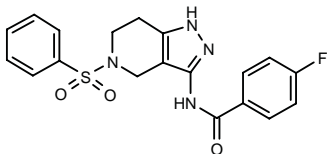


C10 H16 N4 O2; Mol wt: 224.2624

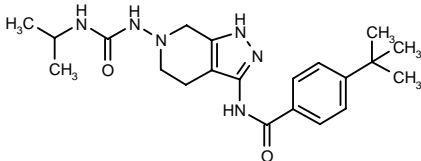
ACTION – An inhibitor of cyclin-dependent kinases (CDKs), as well as other protein kinases including protein kinase C (PKC), Met, PAK-4, PAK-5, ZC-1, STK-2, DDR-2, aurora-1, aurora-2, Bub-1, PLK, Chk1, Chk2, HER2, MAPK, EGFR, PDGFR, etc. Potentially useful for the treatment of cancer, Alzheimer's disease, viral infections, autoimmune diseases, neurodegenerative disorders and proliferative disorders including benign prostatic hyperplasia, familial adenomatosis, polyposis, neurofibromatosis, psoriasis, atherosclerosis, pulmonary fibrosis, arthritis, glomerulonephritis, postsurgical stenosis and restenosis. Other exemplified bicyclic pyrazole compounds include the following:



Compound	R1	R2=R3	R4	R5	Formula
317299	COCH2Ph	H	H	COCH2Ph	C ₂₁ H ₂₀ N ₄ O ₂
317300	Ac	H	H	2-furyl-CO	C ₁₂ H ₁₂ N ₄ O ₃
317309	COCH2Ph	Me	H	2-Naph-CH2CO	C ₂₇ H ₂₆ N ₄ O ₂
317319	t-BuOCO	H	CO2Et	H	C ₁₃ H ₂₀ N ₄ O ₄
317320	H	H	CO2Et	2-Naph-CH(Me)CO	C ₂₁ H ₂₂ N ₄ O ₃



317303: C19 H17 F N4 O3 S



317318: C21 H30 N6 O2

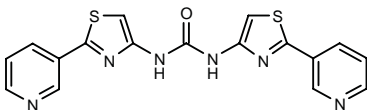
SOURCE – Pharmacia.

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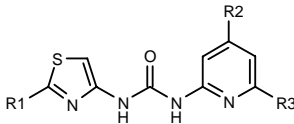
317720

*N*¹,*N*³-Bis[2-(3-pyridyl)thiazol-4-yl]urea



C17 H12 N6 O S2; Mol wt: 380.4548

ACTION – Tyrosine kinase inhibitor, potentially useful for the treatment of conditions associated with cell proliferation and apoptosis such as cancer and neurological disorders, particularly stroke. Other exemplified urea-containing compounds include the following:



Compound	R1	R2	R3	Formula
317721	4-Pyr	H	N(Et)2	C ₁₈ H ₂₀ N ₆ OS
317722	2-Pyr	Et	H	C ₁₆ H ₁₅ N ₅ OS
317723	4-Pyr	H	3-[N(Et)2CO]-1-Pip-CH2	C ₂₅ H ₃₁ N ₇ O ₂ S
317724	4-Pyr	H	4-(HOCH2CH2NH)-1-Pip-CH2	C ₂₂ H ₂₇ N ₇ O ₂ S
317725	4-Pyr	H	CONHCH2CH2N(Me)2	C ₁₉ H ₂₁ N ₇ O ₂ S
317726	4-Pyr	H	4-(2-Pyr)-1-Piz	C ₂₃ H ₂₂ N ₈ OS
317727	4-Pyr	H	4-oxo-1-Pip-CH2	C ₂₀ H ₂₀ N ₆ O ₂ S
317728	1,3-benzodioxol-5-yl	H	1-Pip-CH2	C ₂₂ H ₂₃ N ₅ O ₃ S

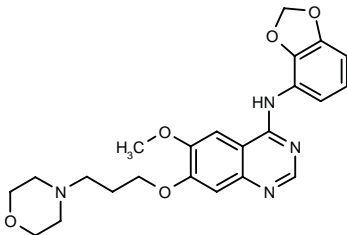
SOURCE – Amgen.

REFERENCES

1. Santora, V. et al. (Amgen Inc.) *Urea cpds. and methods of use.* WO 0214311.

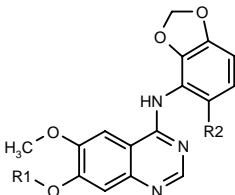
317976

N-(1,3-Benzodioxol-4-yl)-6-methoxy-7-[3-(4-morpholinyl)-propoxy]quinazolin-4-amine



C23 H26 N4 O5; Mol wt: 438.4814

ACTION – Inhibitor of nonreceptor tyrosine kinases of the Src family including c-Src, c-Yes and c-Fyn, potentially useful for the prevention and treatment of solid tumors. Other specifically claimed quinazoline derivatives include the following:



Compound	R1	R2	Formula
317977	4-Me-1-Piz-CH2CH2	H	C ₂₃ H ₂₇ N ₅ O ₄
317978	1-Me-4-Pip-CH2	H	C ₂₃ H ₂₈ N ₄ O ₄
317979	i-PrN(Me)CH2CH(OH)CH2	H	C ₂₃ H ₂₈ N ₄ O ₅
317980	4-Me-1-Piz-CH2CH2OCH2CH2	H	C ₂₅ H ₃₁ N ₅ O ₅
317981	1-pyrrolidinyl-(CH2)3	Cl	C ₂₃ H ₂₅ ClN ₄ O ₄
317982	1-Me-4-Pip-CH2CH2	H	C ₂₄ H ₂₈ N ₄ O ₄
317983	2-CN-4-Pyr-CH2	Cl	C ₂₃ H ₁₆ ClN ₅ O ₄
317984	1-Me-4-Pip-CH2	Cl	C ₂₃ H ₂₅ ClN ₄ O ₄

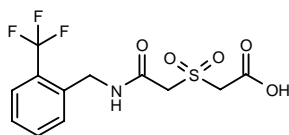
SOURCE – AstraZeneca.

REFERENCES

1. Hennequin, L.F.A. et al. (AstraZeneca plc; AstraZeneca AB) *Quinazoline derivs.* WO 0216352.

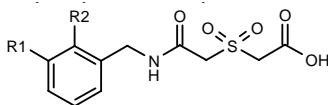
318208

2-[N-[2-(Trifluoromethyl)benzyl]carbamoylmethylsulfonyl]acetic acid



C12 H12 F3 N O5 S; Mol wt: 339.2888

ACTION – Potent small-molecule inhibitor of fumaryl-acetoacetate hydrolase (fumarylacetoacetase; IC_{50} = 5 nM) with favorable biopharmaceutical properties and potentially useful for the treatment of non-small cell lung



Compound	R1	R2	Formula
318206	CF3	H	C ₁₂ H ₁₂ F ₃ NO ₅ S
318210	-CH=CHCH=CH-		C ₁₅ H ₁₅ NO ₅ S

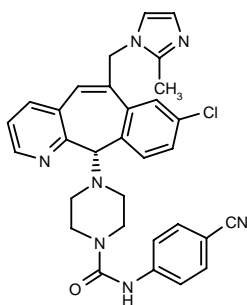
SOURCE – Bayer.

REFERENCES

1. Dumas, J. *Fumaryl acetoacetate hydrolase inhibitors for the treatment of cancer.* 223rd ACS Natl Meet (April 7-11, Orlando) 2002, Abst MEDI 218.

318269

4-[8-Chloro-6-(2-methyl-1*H*-imidazol-1-ylmethyl)-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11(*S*)-yl]-*N*-(4-cyano-phenyl)piperazine-1-carboxamide



C31 H28 Cl N7 O; Mol wt: 550.0632

ACTION – A representative compound from a series of inhibitors of protein farnesyltransferase, potentially useful for the treatment of proliferative diseases such as cancer. Compound was able to reduce tumor growth in mice bearing murine *H-ras*-transformed fibroblasts, human non-small cell lung cancer HTB-177 cells and human melanoma LOX cells.

SOURCES – Pharmacopeia; Schering-Plough.

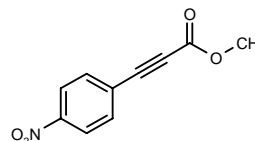
REFERENCES

1. Njoroge, F.G. et al. (Schering Corp.; Pharmacopeia, Inc.) *Tricyclic antitumor cpds. being farnesyl protein transferase inhibitors.* WO 0218368.

B17

317186

3-(4-Nitrophenyl)-2-propynoic acid methyl ester



C10 H7 N O4; Mol wt: 205.1683

ACTION – A representative compound from a series of unsaturated erbB-2 (HER2) tyrosine kinase inhibitors with potential as antitumor agents. B17 inhibited erbB-2 kinase *in vitro* with an IC_{50} value of 1-2 μ M, and exhibited > 100-fold selectivity over epidermal growth factor receptor (EGFR) kinase. This compound was shown to inhibit the growth of MDA-MB-453 and 3T3 cells overexpressing erbB-2, while having only residual effects on the growth of cells overexpressing EGFR kinase. ErbB-2 phosphorylation was also inhibited *in vivo* by this compound in mice bearing BT-474 xenografts. A 28% reduction in tumor volume was observed following i.p. administration at a dose of 100 mg/kg twice per week.

SOURCE – Georgetown University, Washington, DC (US).

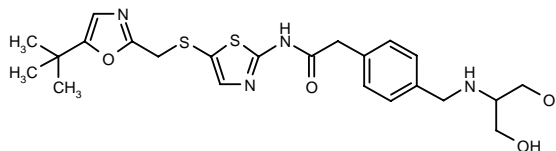
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1. Shaomeng, W. et al. (Georgetown University) *erbB-2 selective small molecule kinase inhibitors.* WO 0209684.

BMS-419437

306645

N-[5-(5-*tert*-Butyloxazol-2-ylmethylsulfanyl)thiazol-2-yl]-2-[4-[2-hydroxy-1-(hydroxymethyl)ethylaminomethyl]-phenyl]acetamide



C23 H30 N4 O4 S2; Mol wt: 490.6460

ACTION – Antineoplastic agent, a potent and selective cyclin-dependent kinase (CDK) inhibitor active against CDK2/cyclin E (IC_{50} = 3 nM), with 10-30-fold selectivity over CDK1/cyclin B and CDK4/cyclin D (IC_{50} = 30 and 102 nM, respectively) and > 1,000-fold selectivity over a range of other kinases. Compound showed strong cytotoxicity in human ovarian carcinoma A2780 cells (IC_{50} = 29 nM) and strong antitumor efficacy in the A2780 xenograft model in mice.

SOURCE – Bristol-Myers Squibb.

REFERENCES

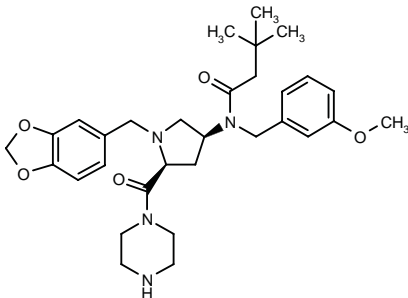
1. Kim, K.S. et al. (Bristol-Myers Squibb Co.) *N*-[5-[[[5-Alkyl-2-oxazolyl]methyl]thio]-2-thiazolyl]-carboxamide inhibitors of cyclin dependent kinases. WO 0144241.

2. Misra, R.N. et al. *Discovery and development of acyl-2-aminothiazole cyclin-dependent kinase inhibitors with potent in vivo anti-tumor activity*. 223rd ACS Natl Meet (April 7-11, Orlando) 2002, Abst MEDI 251.

CUR-61414

305810

N-[1-(1,3-Benzodioxol-5-ylmethyl)-5(*S*)-(piperazin-1-ylcarbonyl)pyrrolidin-3(*S*)-yl]-*N*-(3-methoxybenzyl)-3,3-dimethylbutyramide



C31 H42 N4 O5; Mol wt: 550.6958

ACTION – Small-molecule inhibitor of the hedgehog signaling pathway found to inhibit the proliferation of and induce apoptosis in basal cell carcinoma models, causing regression of the lesions, while having no effect on normal mouse skin. Compound is under phase I clinical evaluation for the therapy of basal cell carcinoma.

SOURCE – Curis.

REFERENCES

1. Baxter, A.D. et al. (Curis, Inc.) *Mediators of hedgehog signaling pathways, compsns. and uses related thereto*. WO 0126644.

2. Pepicelli, C.V. and Campbell, J. Jr. *Hedgehog antagonists induce regression of basal cell carcinoma*. 60th Annu Meet Am Acad Dermatol (Feb 22-27, New Orleans) 2002, Abst P21.

3. Williams, J.A. et al. *A novel hedgehog antagonist as a chemotherapeutic for basal cell carcinoma*. Proc Am Assoc Cancer Res 2002, (Suppl.): Abst LB-118.

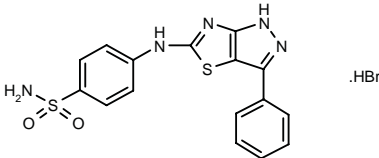
4. *Clinical trial of Cur-61414 commences for treatment of sporadic BCC*. DailyDrugNews.com (Daily Essentials) 2001, Sept 12.

5. *Curis pipeline - Lead products*. Curis Web Site 2001, Feb 27

ANGIOGENESIS INHIBITORS

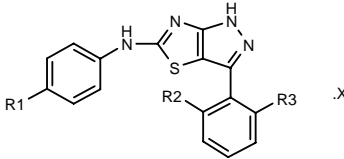
317106

4-(3-Phenyl-1*H*-pyrazolo[3,4-*d*]thiazol-5-ylamino)-benzenesulfonamide hydrobromide



C16 H13 N5 O2 S2 . HBr; Mol wt: 452.3556

ACTION – An inhibitor of cyclin-dependent kinases, particularly CDK2 and/or CDK4, with K_i values of 390 and 34 nM, respectively, against CDK4/cyclin D3 and CDK2/cyclin A. Potentially useful for the treatment of conditions associated with unwanted angiogenesis including cancer, mycotic infection, diabetic retinopathy, glaucoma, rheumatoid arthritis, restenosis and psoriasis. Other exemplified pyrazolo[3,4-*d*]thiazole compounds are:



Compound	R1	R2	R3	X	Formula
317107	OMe	H	H	HBr	C17H14N4OS.HBr
317108	SO2NH2	F	F		C16H11F2N5O2S2
317109	4-Me-1-Piz	H	H	HBr	C21H22N6S.HBr

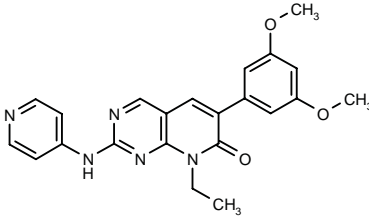
SOURCE – Agouron (Pfizer).

REFERENCES

1. Chong, W.K.M. and Duvadie, R.K. (Agouron Pharmaceuticals, Inc.) *Pyrazole-thiazole cpds., pharmaceutical compsns. containing them, and methods of their use for inhibiting cyclin-dependent kinases*. WO 0212250.

317110

6-(3,5-Dimethoxyphenyl)-8-ethyl-2-(pyridin-4-ylamino)-pyrido[2,3-*d*]pyrimidin-7(8*H*)-one



C22 H21 N5 O3; Mol wt: 403.4399

ACTION – A representative compound from a series of pyrido[2,3-*d*]pyrimidin-7-one derivatives with antiangiogenic properties. It is selective for vascular endothelial growth factor VEGFR-2 and fibroblast growth factor FGFR-1 kinases and demonstrated a half-life of > 200 min in *in vitro* studies. It was active and well tolerated in a murine mammary adenocarcinoma model at doses of 5-40 mg/kg administered by oral gavage. Potentially useful for the treatment of hyperproliferative disorders such as cancer, atherosclerosis, rheumatoid arthritis and psoriasis.

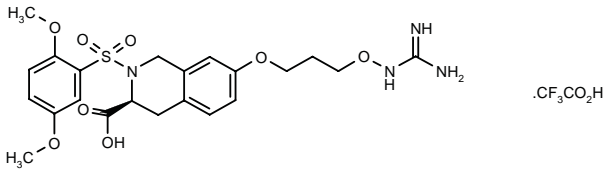
SOURCE – Pfizer.

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1. Hamby, J.M. et al. (Pfizer Inc.) 2-(4-Pyridyl)amino-6-dialkoxyphenyl-pyrido[2,3-*d*]pyrimidin-7-ones. WO 0212238.

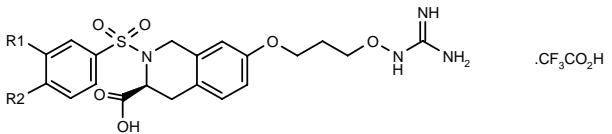
317211

2-(2,5-Dimethoxyphenylsulfonyl)-7-[3-(guanidinooxy)-propoxy]-1,2,3,4-tetrahydroisoquinoline-3(*S*)-carboxylic acid trifluoroacetate



C22 H28 N4 O8 S . C2 H F3 O2; Mol wt: 622.5711

ACTION – An inhibitor of integrins, particularly $\alpha_v\beta_3$ and $\alpha_v\beta_5$, proven to inhibit the interaction of vitronectin and $\alpha_v\beta_3$ *in vitro* with an IC₅₀ of 73 nM. Potentially useful for the treatment of cancer, osteoporosis, restenosis, inflammation, macular degeneration, diabetic retinopathy and rheumatoid arthritis. Other exemplified tetrahydroisoquinoline-3-carboxylic acid derivatives are:



Compound	R1	R2	Formula
317212	H	H	C ₂₀ H ₂₄ N ₄ O ₆ S.C ₂ HF ₃ O ₂
317213	-CH=CHCH=CH-		C ₂₄ H ₂₆ N ₄ O ₆ S.C ₂ HF ₃ O ₂

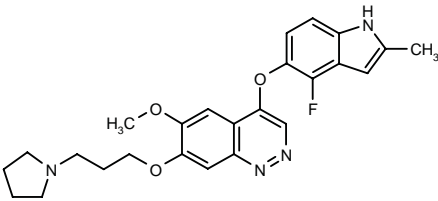
SOURCE – 3-Dimensional Pharmaceuticals.

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1. Wang, A. (3-Dimensional Pharmaceuticals, Inc.) Tetrahydroisoquinoline-3-carboxylic acid alkoxyguanidines as integrin antagonists. WO 0212193.

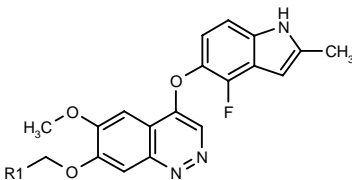
317378

4-(4-Fluoro-2-methyl-1*H*-indol-5-yloxy)-6-methoxy-7-[3-(1-pyrrolidinyl)propoxy]cinnoline



C25 H27 F N4 O3; Mol wt: 450.5113

ACTION – Antiangiogenic agent that inhibits the effects of vascular endothelial growth factor (VEGF). Potentially useful for the treatment of cancer and rheumatoid arthritis. Other specifically claimed compounds are:



Compound	R1	Formula
317379	4-Pip	C ₂₄ H ₂₅ FN ₄ O ₃
317380	(<i>R</i>)-1-Pip-CH ₂ CH(OH)	C ₂₆ H ₂₉ FN ₄ O ₄
317381	1-Me-4-Pip	C ₂₅ H ₂₇ FN ₄ O ₃
317382	Ph	C ₂₅ H ₂₀ FN ₃ O ₃
317383	(<i>R</i>)-1-pyrrolidinyl-CH ₂ CH(OH)	C ₂₅ H ₂₇ FN ₄ O ₄
317384	4-Me-1-Piz-CH ₂ CH ₂	C ₂₆ H ₃₀ FN ₅ O ₃
317385	1-Pip-CH ₂ CH ₂	C ₂₆ H ₂₉ FN ₄ O ₃

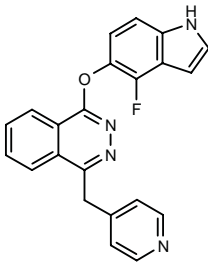
SOURCE – AstraZeneca.

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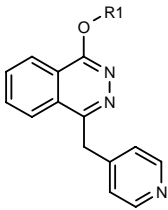
317386

1-(4-Fluoro-1*H*-indol-5-yloxy)-4-(pyridin-4-ylmethyl)-phthalazine

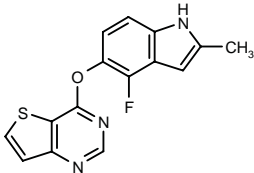


C22 H15 F N4 O; Mol wt: 370.3855

ACTION – Antiangiogenic agent that inhibits the effects of vascular endothelial growth factor (VEGF). Potentially useful for the treatment of cancer and rheumatoid arthritis. Other specifically claimed compounds are:



Compound	R1	Formula
317387	6-indolyl	C ₂₂ H ₁₆ N ₄ O
317388	2-Me-6-indolyl	C ₂₃ H ₁₈ N ₄ O
317390	2-Me-4-F-5-indolyl	C ₂₃ H ₁₇ FN ₄ O



317389: C15 H10 F N3 O S

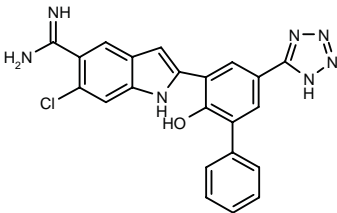
SOURCE – AstraZeneca.

REFERENCES

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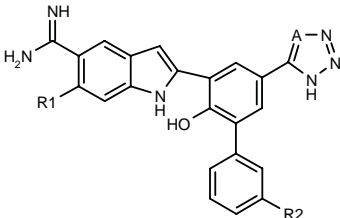
317699

6-Chloro-2-[2-hydroxy-5-(1*H*-tetrazol-5-yl)biphenyl-3-yl]-1*H*-indole-5-carboxamide



C22 H16 Cl N7 O; Mol wt: 429.8694

ACTION – Selective urokinase-type plasminogen activator (uPA) inhibitor with desirable pharmacokinetic features. Potentially useful for the treatment of cancer. Other specifically claimed compounds are:



Compound	R1	R2	A	Formula
317700	F	H	N	C ₂₂ H ₁₆ FN ₇ O
317702	F	NO2	N	C ₂₂ H ₁₅ FN ₈ O ₃
317703	Cl	NO2	N	C ₂₂ H ₁₅ ClN ₈ O ₃
317704	Cl	NO2	CH	C ₂₃ H ₁₆ ClN ₇ O ₃
317706	Cl	H	CH	C ₂₃ H ₁₇ ClN ₆ O
317707	F	H	CH	C ₂₃ H ₁₇ FN ₆ O
317708	F	NO2	CH	C ₂₃ H ₁₆ FN ₇ O ₃

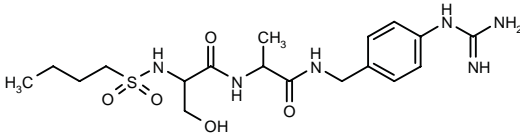
SOURCE – Celera Genomics.

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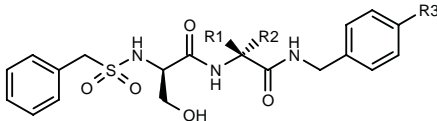
317763

N-(Butylsulfonyl)-DL-seryl-DL-alanine *N*-(4-guanidinobenz-yl)amide

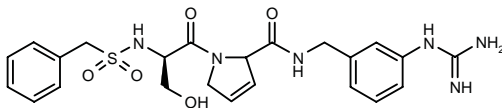


C18 H30 N6 O5 S; Mol wt: 442.5380

ACTION – Antiangiogenic agent that acts as a noncovalent inhibitor of urokinase-type plasminogen activator (uPA). Compound gave an IC₅₀ of < 100 nM against uPA *in vitro* and exhibited selectivity over other serine proteases such as tissue plasminogen activator (tPA) and plasmin. Potentially useful for the prevention of metastasis, neovascularization and degradation of extracellular matrix in tumors and other neoplasms, as well as other disorders associated with pathological neovascularization including retinopathies and inflammatory conditions such as stroke and transplant rejection. Other exemplified compounds include the following:



Compound	R1	R2	R3	Formula
317764		-O-	t-BuOCONHC(=NH)	C ₂₈ H ₃₁ N ₅ O ₈ S
317765	Me	H	NHC(=NH)NH2	C ₂₁ H ₂₈ N ₆ O ₅ S



317766: C23 H28 N6 O5 S

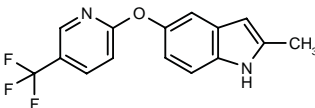
SOURCE – Corvas.

REFERENCES

1. Levy, O.E. et al. (Corvas International, Inc.) *Non-covalent inhibitors of urokinase and blood vessel formation.* EP 1182207, WO 0214349.

317884

2-Methyl-5-[5-(trifluoromethyl)pyridin-2-yloxy]-1*H*-indole



C15 H11 F3 N2 O; Mol wt: 292.2589

ACTION – Vascular endothelial growth factor (VEGF) inhibitor, potentially useful for the treatment of disorders associated with angiogenesis and/or increased vascular permeability, particularly solid tumors, and also rheumatoid arthritis, diabetes, psoriasis, Kaposi’s sarcoma, hemangioma, acute and chronic nephropathies, atheroma, arterial restenosis, autoimmune diseases, acute inflammation, excessive scar formation and adhesion, lymphedema, endometriosis, dysfunctional uterine bleeding and ocular diseases with retinal vessel proliferation.

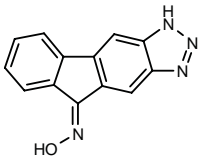
SOURCE – AstraZeneca.

REFERENCES

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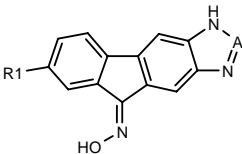
317898

Fluoreno[2,3-*d*][1,2,3]triazol-9(3*H*)-one oxime



C13 H8 N4 O; Mol wt: 236.2332

ACTION – Protein kinase inhibitor giving *K_i* values of 0.213, 0.680, 1.47 and 0.571 μ M, respectively, against CDK4/cyclin D3, CDK2/cyclin A, VEGFR and CHK-1. In addition, compound was able to inhibit the proliferation of human colon carcinoma HCT 116 (*IC*₅₀ = 10.4 μ M), human osteogenic sarcoma U-2 OS (*IC*₅₀ = 18.0 μ M) and human osteogenic sarcoma Saos-2 cells (*IC*₅₀ = 11.0 μ M). Potentially useful for the treatment of cancer and other angiogenesis-related disorders including diabetic retinopathy, glaucoma, rheumatoid arthritis and psoriasis. Other exemplified heterocyclic fluorene oximes are:



Compound	R1	A	Formula
317899	H	CH	C ₁₄ H ₉ N ₃ O
317900	H	C(NH2)	C ₁₄ H ₁₀ N ₄ O
317901	I	N	C ₁₃ H ₇ IN ₄ O

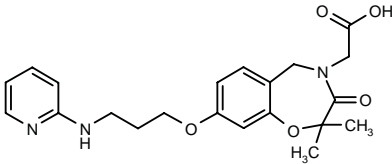
SOURCE – Agouron (Pfizer).

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1. Chong, W.K.M. and Duvadie, R.K. (Agouron Pharmaceuticals, Inc.) *Heterocyclic-hydroxyimino-fluorenes and their use for inhibiting protein kinases.* WO 0216326.

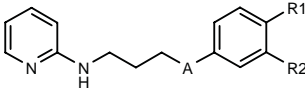
318200

2-[2,2-Dimethyl-3-oxo-8-[3-(pyridin-2-ylamino)propoxy]-2,3,4,5-tetrahydro-1,4-benzoxazepin-4-yl]acetic acid

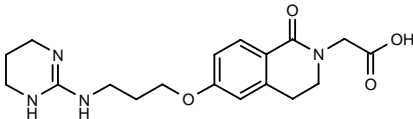


C21 H25 N3 O5; Mol wt: 399.4445

ACTION – Integrin $\alpha_v\beta_3$ and/or $\alpha_v\beta_5$ receptor antagonist, potentially useful for the treatment of cancer, angiogenesis, osteoporosis, humoral hypercalcemia, smooth muscle cell migration, restenosis, atherosclerosis, macular degeneration, retinopathy and arthritis. Other specifically claimed bicyclic compounds are:



Compound	R1,R2	A	Formula
318203	-CH2N(CH2CH2CO2H)CH2CH2-	O	C ₂₀ H ₂₅ N ₃ O ₃
318204	-N(CH2CO2H)CH=CH-	O	C ₁₈ H ₁₉ N ₃ O ₃
318205	-CH2CH(CH2CO2H)CH2-	O	C ₁₉ H ₂₂ N ₂ O ₃
318207	-CON(CH2CO2H)CH2CH2O-	O	C ₁₉ H ₂₁ N ₃ O ₅
318209	-CH2N(CH2CO2H)CH2CH2O-	O	C ₁₉ H ₂₃ N ₃ O ₄
318213	-CH2CH(CH2CO2H)CH2O-	O	C ₁₉ H ₂₂ N ₂ O ₄
318214	-CH2CH(CH2CO2H)CH2CH2-	S	C ₂₀ H ₂₄ N ₂ O ₂ S



318211: C18 H24 N4 O4

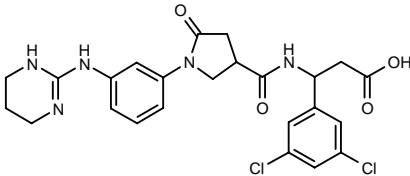
SOURCE – Pharmacia.

REFERENCES

1. Ish, K.K. et al. (Pharmacia Corp.) *Cpds. containing a bicyclic ring system useful as $\alpha_v\beta_3$ antagonists.* WO 0218377.

318217

3-(3,5-Dichlorophenyl)-3-[5-oxo-1-[3-(1,4,5,6-tetrahydropyrimidin-2-ylamino)phenyl]pyrrolidin-3-ylcarboxamido]-propionic acid



C24 H25 Cl2 N5 O4; Mol wt: 518.3985

ACTION – Dual antagonist of integrin $\alpha_v\beta_3$ and integrin $\alpha_v\beta_5$ (*K_i* = 18.6 and 22.1 nM, respectively) with selectivity over the gp11b/IIIa receptor (*K_i* > 25 μ M) and a favorable pharmacokinetic profile in rats. Potentially useful for the treatment of osteoporosis, cancer and ocular diseases.

SOURCE – Amgen.

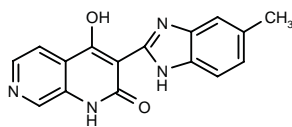
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1. Dominguez, C. et al. (Amgen Inc.) 1-(Aminophenyl)-2-pyrrolidones as integrin inhibitors. WO 0144230.

2. Xi, N. et al. Aromatic and alkyl ureas as guanidine mimetics in integrin $\alpha_v\beta_3$ antagonists. 223rd ACS Natl Meet (April 7-11, Orlando) 2002, Abst MEDI 189.

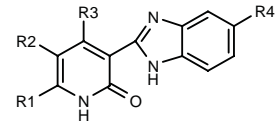
318231

4-Hydroxy-3-(5-methyl-1*H*-benzimidazol-2-yl)-1,7-naphthyridin-2(1*H*)-one



C16 H12 N4 O2; Mol wt: 292.2968

ACTION – Vascular endothelial growth factor (VEGF) receptor tyrosine kinase inhibitor, expected to be useful for the treatment of angiogenesis-related disorders, particularly cancer. Other exemplified heterocyclic compounds include the following:



Compound	R1	R2	R3	R4	Formula
318232	-CH=NCH=CH-	NH2		4-Me-1-Piz	C ₁₄ H ₁₀ N ₄ OS
318233	-CH=CHN=CH-	NH2		4-morpholinyl	C ₁₄ H ₁₀ N ₄ OS
318234	-CH=CHCH=N-	NH2		3-[N(Me)2]-1-pyrrolidinyl	C ₁₄ H ₁₀ N ₄ OS
318235	-CH=CHCH=N-	NH2		4-Me-1-Piz	C ₁₄ H ₁₀ N ₄ OS
318236	-N=CHCH=CH-	OH		H	C ₁₄ H ₁₀ N ₄ OS
318237	-SCH=CH-	NH2		H	C ₁₄ H ₁₀ N ₄ OS
318238	-NH-CH=N-	NH2		H	C ₁₃ H ₁₀ N ₆ O
318239	-N(Me)N=CH-	NH2		H	C ₁₄ H ₁₂ N ₆ O

SOURCE – Chiron.

REFERENCES

1. Renhowe, P. et al. (Chiron Corp.) *Heterocyclic cpds.* WO 0218383.

T-8

318516

L-Lysyl-L-glutaminyl-L-arginyl-L-phenylalanyl-L-threonyl-L-threonyl-L-methionyl-L-prolyl-L-phenylalanyl-L-leucyl-L-phenylalanyl-L-cysteinyl-L-asparaginyl-L-valyl-L-asparaginyl-L-aspartyl-L-valyl-L-cysteinyl-L-asparaginyl-L-phenylalanyl-L-alanyl-L-seryl-L-arginyl-L-asparaginyl-L-aspartyl-L-tyrosyl-L-serine

C141 H209 N39 O42 S3; Mol wt: 3218.6310

ACTION – Antiangiogenic agent, a smaller synthetic peptide derivative of tumstatin able to selectively inhibit the serum-stimulated proliferation of calf pulmonary aortic endothelial cells with an IC₅₀ of 13.4 µg/ml, while having little effect on nonendothelial cells (IC₅₀ > 50 µg/ml). The peptide also produced apoptosis in endothelial cells at 50 µg/ml. In a Matrigel plug angiogenesis model in mice, systemically administered compound inhibited neovascularization in a dose-dependent manner, with maximal activity seen at a dose of 15 mg/kg. In mice bearing human breast cancer MDA-MB-435 and prostate cancer PC-3 xenografts, a dose of 5 mg/kg/day i.p. for 21 days reduced tumor growth by 50.5 and 35.4%, respectively; a dose-dependent reduction in tumor microvascular density was also seen. Selected as a candidate for further preclinical and clinical evaluation.

SOURCES – Beth Israel Deaconess Medical Center, Boston, MA (US); Ilex Oncology.

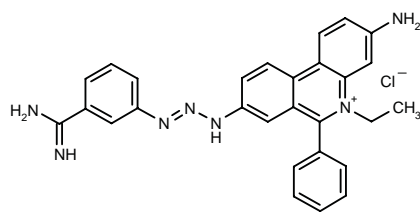
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1. Reimer, C.L. et al. T8, a synthetic peptide derived from tumstatin that retains antiangiogenic and antitumorigenic activity. Proc Am Assoc Cancer Res 2002, 43: Abst 4188.

OTHER ONCOLYTIC DRUGS

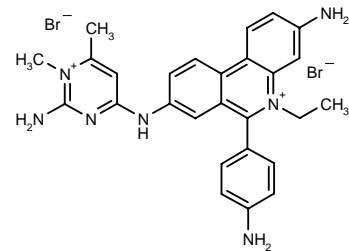
317047

8-[1-(3-Amidinophenyl)triazen-3-yl]-3-amino-5-ethyl-6-phenylphenanthridinium chloride



C28 H26 Cl N7; Mol wt: 496.0154

ACTION – Antineoplastic agent with telomerase-inhibitory activity (IC₅₀ = 0.019 µM); it inhibited the growth of human lung cancer A549 cells with an IC₅₀ of 3.38 µM. Another exemplified compound within this series of phenanthridine derivatives is:



317050: C27 H29 Br2 N7

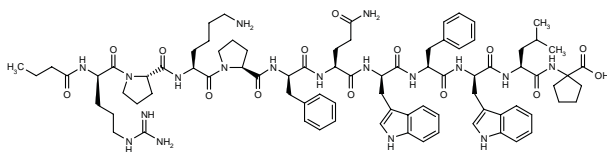
SOURCE – Aventis Pharma.

REFERENCES

1. Mailliet, P. et al. (Aventis Pharma SA) *Phenanthridine derivs. and their use as anti-telomerase agent.* WO 0212194.

317240

1-(*N*²-Butyryl-D-arginyl-L-prolyl-L-lysyl-L-prolyl-D-phenylalanyl-L-glutamyl-D-tryptophyl-L-phenylalanyl-D-tryptophyl-L-leucylamino)cyclopentanecarboxylic acid



C83 H112 N18 O14; Mol wt: 1585.9100

ACTION – Substance P antagonist with *in vitro* activity against a panel of human cancer cell lines. Compound displayed activity when administered i.v. to mice bearing human colon adenocarcinoma PCT xenografts; treatment with a daily dose of 8.5 µg/animal for 10 days resulted in 78.54% inhibition of tumor growth compared to controls.

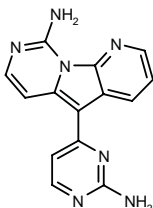
SOURCE – Dabur Research Foundation, Uttar Pradesh (IN).

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1. Cord, J.I. et al. (Dabur Research Foundation) *Substance P analogs for the treatment of cancer*. WO 0210194.

317274

5-(2-Aminopyrimidin-4-yl)pyrido[3',2':4,5]pyrrolo[1,2-c]-pyrimidin-9-amine



C14 H11 N7; Mol wt: 277.2899

ACTION – Variolin B analogue with antitumor activity, shown to display cytotoxic activity against murine leukemia P388, human lung carcinoma A549 and human colon adenocarcinoma HT-29 cells lines with respective IC₅₀ values of 0.36, 0.04 and 0.04 µM.

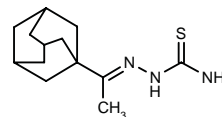
SOURCE – Universitat de Barcelona, Barcelona (ES).

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1. Alvarez, M. et al. (Universitat de Barcelona) *Derivs. of variolin B*. WO 0212240.

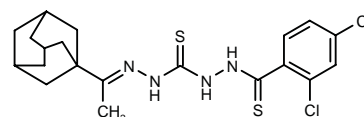
317282

1-(1-Adamantyl)ethanone thiosemicarbazone



C13 H21 N3 S; Mol wt: 251.3959

ACTION – Thiosemicarbazone derivative with antitumor activity against a range of established human leukemia cell lines (IC₅₀ = 2.8-23.6 µM). Compound showed no antiviral or antibacterial activity against a panel of viruses and bacteria at nontoxic concentrations. Another related compound is:



317283: C20 H24 Cl2 N4 S2

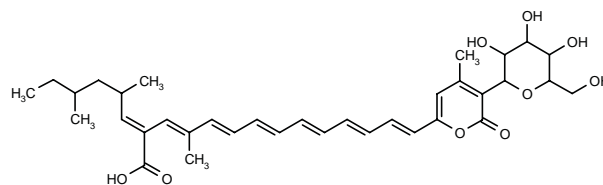
SOURCES – University of Athens, Athens (GR); International Institute of Anticancer Research, Kapandriti (GR); Katholieke Universiteit Leuven, Leuven (BE).

REFERENCES

1. Kolocouris, A. et al. *New 2-(1-adamantylcarbonyl)pyridine and 1-acetyladamantane thiosemicarbazones-thiocarbonohydrazones: Cell growth inhibitory, antiviral and antimicrobial activity evaluation*. Bioorg Med Chem Lett 2002, 15(5): 723.

317622

2-(2,4-Dimethylhexylidene)-4-methyl-14-[3,4,5-trihydroxy-6-(hydroxymethyl)-4'-methyl-2'-oxo-3,4,5,6-tetrahydro-2*H*,2'-*H*-2,3'-bipyran-6'-yl]tetradeca-3,5,7,9,11,13-hexaenoic acid



C35 H46 O9; Mol wt: 610.7394

ACTION – Telomerase inhibitor isolated from cultures of *Epicoccum purpurascens* D8646 strain (FERM P-17859). The compound displayed an IC₅₀ of 67 µM against telomerase from human ovarian teratocarcinoma PA-1 cells. By virtue of its activity, this compound is considered to have potential in the treatment of solid and nonsolid tumors.

SOURCE – Mitsubishi Pharma.

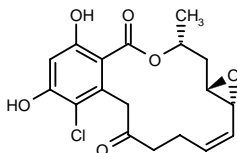
REFERENCES

1. Kimura, J. et al. (Mitsubishi-Tokyo Pharmaceuticals, Inc.) *Telomerase inhibitors*. JP 2002047281.

317928

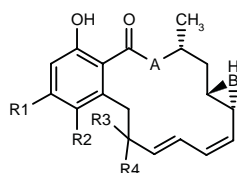
(1*aR*,14*R*,15*aS*)-8-Chloro-9,11-dihydroxy-14-methyl-4,5,6,7,12,14,15,15*a*-octahydro-1*aH*-oxireno[*e*][2]-benzoxacyclotetradecin-6,12-dione

(3*R*,5*S*,6*R*)-13-Chloro-5,6-epoxy-14,16-dihydroxy-3-methyl-3,4,5,6,9,10,11,12-octahydro-1*H*-2-benzoxacyclopentadecin-1,11-dione

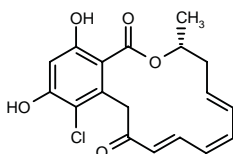


C18 H19 Cl O6; Mol wt: 366.7951

ACTION – Antitumor agent, particularly useful for the treatment of glioblastoma, retinoblastoma and small cell lung cancer. Other exemplified macrocyclic compounds include the following:



Compound	R1	R2	R3	R4	A	B	Formula
317932	OH	Cl	-S(CH2)3S-		NH	O	C ₂₁ H ₂₄ ClNO ₄ S ₂
317933	OH	Cl	-CH2-		O	O	C ₁₉ H ₁₉ ClO ₅
317934	OH	Cl	H	H	O	O	C ₁₈ H ₁₉ ClO ₅
317935	H	Cl		-O-	O	O	C ₁₈ H ₁₇ ClO ₅
317937	OH	H		-O-	O	CH2	C ₁₉ H ₂₀ O ₅
317940	OH	Cl		-O-	NH	O	C ₁₈ H ₁₈ ClNO ₅
318010	OH	Cl		-O-	O	CH2	C ₁₉ H ₁₉ ClO ₅



317939: C18 H17 Cl O5

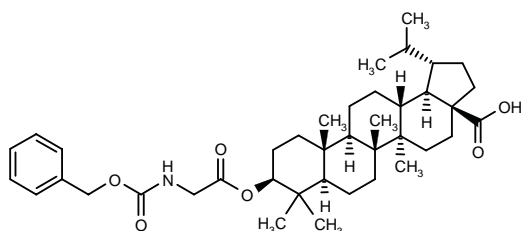
SOURCE – Sloan-Kettering Institute for Cancer Research, New York, NY (US).

REFERENCES

1. Danishefsky, S.J. et al. (Sloan-Kettering Institute) *Novel macrocycles and uses thereof*. WO 0216369.

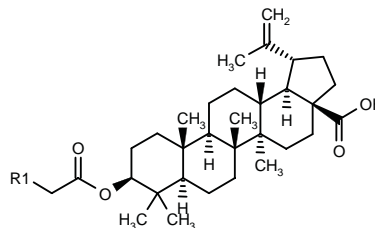
317958

3β-[*N*-(Benzyloxycarbonyl)glycyloxy]lupan-28-oic acid



C40 H59 N O6; Mol wt: 649.9071

ACTION – Antitumor agent with IC₅₀ values of 1.6 µg/ml (dissolved in DMSO) and 2.8 µg/ml (with tissue culture media) against melanoma Mel2 cells. Potentially useful for the treatment of cancer including melanoma, squamous cell tumors, breast cancer, colon cancer, sarcoma, oral epidermal carcinoma, hormone-dependent breast cancer, prostate cancer, lung cancer, glioma and neuroblastoma, as well as for the treatment of HIV infection. Other exemplified compounds within this series of prodrugs of betulinic acid and betulinic acid derivatives are:



Compound	R1	Formula
317959	t-BuOCONH	C ₃₇ H ₅₉ NO ₆
317960	NHCO2CH2Ph	C ₄₀ H ₅₇ NO ₆
317961	OCH2CH2OCH2CH2OMe	C ₃₇ H ₆₀ O ₇

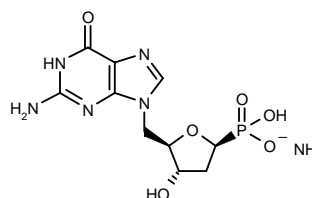
SOURCES – Advanced Life Sciences; University of Illinois, Urbana, IL (US).

REFERENCES

1. Pezzuto, J.M. et al. (University of Illinois;Advanced Life Sciences Inc.) *Prodrugs of betulinic acid derivs. for the treatment of cancer and HIV*. WO 0216395.

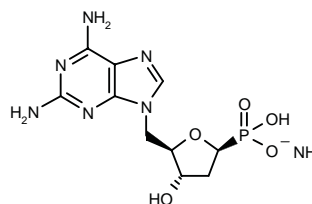
318215

5-(Guanin-9-ylmethyl)-4(*S*)-hydroxytetrahydrofuran-2(*S*)-phosphonic acid ammonium salt



C10 H14 N5 O6 P . NH3; Mol wt: 348.2543

ACTION – Antineoplastic phosphonate nucleoside with potent *in vitro* antiproliferative activity against human non-small cell lung cancer NCI-H460, breast cancer MCF7 and CNS cancer SF-268 cells (IC₅₀ = 0.12-0.67 µM). Another related compound is:



318216: C10 H15 N6 O5 P . NH3

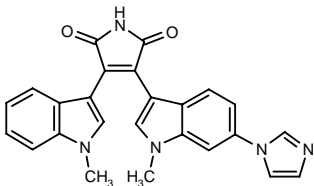
SOURCE – Shire BioChem.

REFERENCES

1. Vaillancourt, L. et al. *Novel antineoplastic phosphonate nucleosides*. 223rd ACS Natl Meet (April 7-11, Orlando) 2002, Abst MEDI 207.

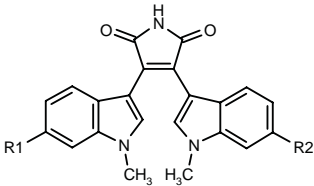
318254

3-[6-(1*H*-imidazol-1-yl)-1-methyl-1*H*-indol-3-yl]-4-(1-methyl-1*H*-indol-3-yl)-1*H*-pyrrole-2,5-dione



C25 H19 N5 O2; Mol wt: 421.4581

ACTION – Orally available cell cycle inhibitor, a derivative of the indolylmaleimide Ro-31-7453 with improved water solubility (1.8 and < 0.01 mg/ml, respectively) and oral bioavailability (31 and 16%, respectively) and similar antiproliferative activity in human breast cancer MDA-MB-45 cells (IC₅₀ = 54 and 22 nM, respectively). Other related compounds are:



Compound	R1	R2	Formula
318249	H	4-morpholinyl	C ₂₆ H ₂₄ N ₄ O ₃
318250	NO ₂	1-pyrrolidinyl	C ₂₆ H ₂₃ N ₅ O ₄
318251	NO ₂	1-Me-2-imidazolyl	C ₂₆ H ₂₀ N ₆ O ₄
318252	NO ₂	1-imidazolyl	C ₂₅ H ₁₈ N ₆ O ₄
318253	OMe	1-imidazolyl	C ₂₆ H ₂₁ N ₅ O ₃

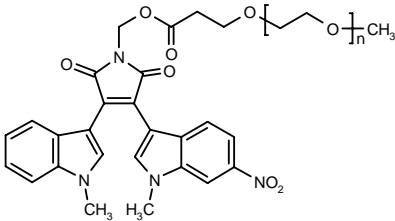
SOURCE – Roche.

REFERENCES

1. Fotouhi, N. et al. (F. Hoffmann-La Roche AG) *Substd. pyrroles*. WO 0146178.
2. Kong, N. et al. *Design and synthesis of novel orally bioavailable, water soluble bisindolylmaleimides as cell cycle inhibitors*. Proc Am Assoc Cancer Res 2002, 43: Abst 3656.

318418

3-(*O*-Methylpolyethyleneglycol)propionic acid 3-(1-methyl-1*H*-indol-3-yl)-4-(1-methyl-6-nitro-1*H*-indol-3-yl)-2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-ylmethyl ester



ACTION – Water-soluble prodrug of the cell cycle inhibitor Ro-31-7453 that contains a polyethylene glycol (PEG) function and an ester linkage. The prodrug showed good oral bioavailability and was rapidly and completely converted to parent compound *in vivo* before entering the bloodstream. In the rat mammary MTLn3 tumor model, it showed comparable activity to Ro-31-7453 following continuous i.v. infusion or oral administration.

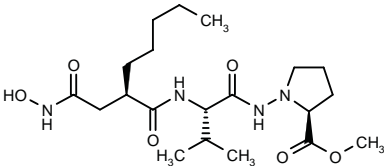
SOURCE – Roche.

REFERENCES

1. Liu, E.A. et al. *A water soluble prodrug for Ro 31-7453 suitable for both oral delivery and continuous infusion*. Proc Am Assoc Cancer Res 2002, 43: Abst 1040.

318419

1-[*N*-[2(*R*)-[*N*-(Hydroxy)carbamoylmethyl]heptanoyl]-*L*-valylamino]-*L*-proline acid methyl ester



C20 H36 N4 O6; Mol wt: 428.5264

ACTION – Actinonin analogue with cytotoxicity in human leukemia HL-60 cells and Daudi lymphoma cells (IC₅₀ = 6.7 and 0.97 μM, respectively).

SOURCE – Memorial Sloan-Kettering Cancer Center, New York, NY (US).

REFERENCES

1. Borella, C. et al. *Asymmetric solid phase and solution parallel synthesis and antitumor properties of actinonin analogs*. Proc Am Assoc Cancer Res 2002, 43: Abst 1032.

ACTION – A representative compound from a group of lipid–peptide conjugates able to inhibit the binding of vasoactive intestinal peptide (VIP) to its receptors, and thus having potential as antitumor agents. DT-B1 was shown to be active *in vitro* against a panel of tumor cell lines. *In vivo*, this compound inhibited the growth of human colon carcinoma PTC xenografts implanted subcutaneously in mice by 95.85% following i.v. treatment at a dose of 25.2 µg/day for 14 days.

SOURCE – Dabur Research Foundation, Uttar Pradesh (IN).

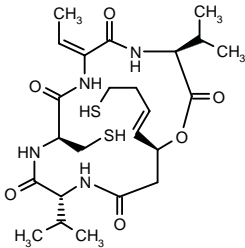
REFERENCES

1. Cord, J.I. et al. (Dabur Research Foundation) *Lipid-peptide conjugates for treatment of cancer*. WO 0210193.

FR-135313

316994

N-[3(S)-Hydroxy-7-sulfanyl-4-heptenoyl]-D-valyl-D-cysteinyl-2-amino-2-butenoyl-L-valine C-1.5-O-3.1-lactone



C24 H38 N4 O6 S2; Mol wt: 542.7182

ACTION – A reduced FK-228 cyclic peptide with histone deacetylase-inhibitory activity (IC₅₀ = 1 µM or less) that enhances transgene expression and may therefore be useful in suicide cancer gene therapy. The use of this compound in the treatment of inflammatory diseases, diabetes and associated complications, homozygous thalassemia, fibrosis, hepatic cirrhosis, acute promyelocytic leukemia (APL), transplant rejection and autoimmune diseases is also described.

SOURCE – Fujisawa.

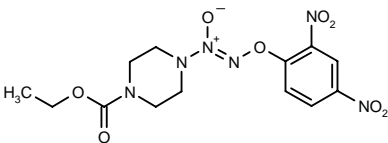
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1. Nakajima, H. et al. (Fujisawa Pharmaceutical Co., Ltd.) *Reduced FK228 and use thereof*. WO 0206307.

JS-K

318424

4-(2,4-Dinitrophenoxy)-NNO-azoxy]piperazine-1-carboxylic acid ethyl ester



C13 H16 N6 O8; Mol wt: 384.3034

ACTION – Antineoplastic agent that inhibited the growth of leukemia HL-60 and prostate cancer PPC-1 cells *in vitro*, and induced differentiation and apoptosis in the leukemia cells. In mice bearing HL-60 or PPC-1 tumors compound at a dose of 4 µmol/kg i.v. 3 times weekly significantly reduced tumor volumes and produced extensive tumor necrosis. In a systemic disease model in mice induced by i.v. injection of HL-60 cells, compound (1 µmol/kg i.v. 3 times weekly for 3 or 4 weeks) decreased leukemia cell engraftment in the bone marrow and liver, and the number and size of enlarged abdominal lymph nodes; 2 of 5 mice were cured at the end of the treatment.

SOURCES – National Cancer Institute, Bethesda, MD (US); University of Utah, Salt Lake City, UT (US); Veterans Administration Medical Center, Hartford, VT (US).

REFERENCES

1. Saavedra, J.E. et al. (US Department of Health & Human Services) *O²-Arylated or O²-glycosylated 1-subst. diazen-1-ium-1,2-diolates and O²-subst. 1-[(2-carboxylato)pyrrolidin-1-yl]diazene-1-ium-1,2-diolates*. WO 9813358.

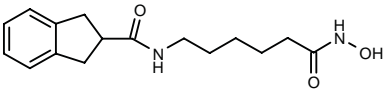
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3. Shami, P.J. et al. *In vivo antineoplastic activity of "JS-K" in NOD-SCID mice*. Proc Am Assoc Cancer Res 2002, 43: Abst 1035.

PX-117735

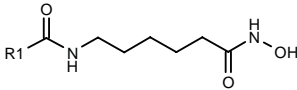
318297

N-[5-(N-Hydroxycarbamoyl)pentyl]indane-2-carboxamide



C16 H22 N2 O3; Mol wt: 290.3608

ACTION – Histone deacetylase (HDAC) inhibitor (IC₅₀ = 6 nM) with antiproliferative activity against human cervical adenocarcinoma HeLa cells and human T-cell leukemia Jurkat cells (IC₅₀ = 0.2 and 0.06 µM, respectively). *In vivo* evaluations showed low toxicity and strong antitumor activity in human tumor xenograft models in mice. Other related compounds are:



Compound	R1	Formula
PX-117456 [318298]	fluoren-9-ylidene=CH	C ₂₁ H ₂₂ N ₂ O ₃
PX-117445 [318299]	2-Naph	C ₁₇ H ₂₀ N ₂ O ₃

SOURCE – Prolifix.

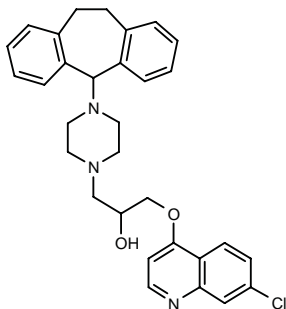
REFERENCES

1. Finn, P. et al. *Discovery and structure-activity relationships of novel classes of histone deacetylase inhibitors*. Proc Am Assoc Cancer Res 2002, 43: Abst 3672.

MODULATORS OF THE THERAPEUTIC ACTIVITY OF ANTINEOPLASTIC AGENTS

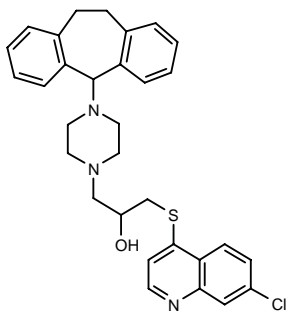
318127

1-(7-Chloroquinolin-4-yloxy)-3-[4-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)piperazin-1-yl]propan-2-ol



C31 H32 Cl N3 O2; Mol wt: 514.0658

ACTION – Agent with the ability to reverse drug resistance, potentially useful for the treatment of multidrug-resistant cancer and infections including malaria, MRSA (methicillin-resistant *Staphylococcus aureus*) infection, etc. It was shown to sensitize multidrug-resistant CHO cell-derived CH(R)C5 cancer cells to mitomycin, and was also able to reverse resistance of MRSA strains to methicillin, cefmetazole and erythromycin. Another exemplified piperazine derivative is:



318128: C31 H32 Cl N3 O S

SOURCE – Pola Chemical.

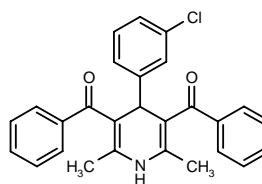
REFERENCES

1. Miyata, Y. et al. (Pola Chemical Industries Inc.) *Piperazine derivs., and agents for the recovery of drug sensitivity*. JP 2002060383.

318546

3,5-Dibenzoyl-4-(3-chlorophenyl)-2,6-dimethyl-1,4-dihydropyridine

[4-(3-Chlorophenyl)-2,6-dimethyl-1,4-dihydro-3,5-pyridinediyl]bis(phenylmethanone)



C27 H22 Cl N O2; Mol wt: 427.9288

ACTION – Multidrug resistance (MDR) reversal agent able to inhibit P-glycoprotein-mediated drug efflux in human MDR1-transfected murine lymphoma L5178 cells; it showed cytotoxic activity comparable to doxorubicin against human oral squamous cell carcinoma ($IC_{50} = 7$ and $1.4 \mu M$, respectively), but a superior selectivity index (> 143 and > 24.4 , respectively) relative to normal fibroblasts.

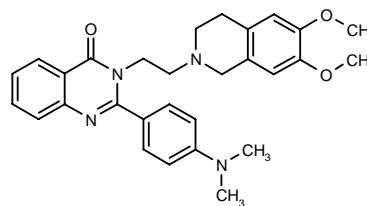
SOURCES – Albert Szent-Györgyi Medical University, Szeged (HU); Humboldt-Universität zu Berlin, Berlin (DE); Josai University, Sakado (JP); Meiji Pharmaceutical University, Tokyo (JP); Saurashtra University, Rajkot (IN).

REFERENCES

1. Gunics, G. et al. *Enhanced antibacterial effect of erythromycin in the presence of 3,5-dibenzoyl-1,4-dihydropyridines*. *Anticancer Res* 2001, 21(1A): 269.
2. Kawase, M. et al. *3,5-Dibenzoyl-1,4-dihydropyridines: Synthesis and MDR reversal in tumor cells*. *Bioorg Med Chem* 2002, 10(4): 1051.

318559

3-[2-(6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl)ethyl]-2-[4-(dimethylamino)phenyl]quinazolin-4(3H)-one



C29 H32 N4 O3; Mol wt: 484.5968

ACTION – Multidrug resistance (MDR) modulator with dual inhibitory activity against P-glycoprotein (Pgp; $IC_{50} = 1.07 \mu M$) and MDR-associated protein (MRP1; $IC_{50} = 1.05 \mu M$). Compound potentiated the cytotoxicity of doxorubicin in MRP-expressing non-small cell lung cancer COR.L23/R cells ($EC_{50} = 3.01$) and in Pgp-expressing mouse mammary carcinoma EMT6/AR1.0 cells ($EC_{50} = 3.3 \mu M$).

SOURCE – Xenova.

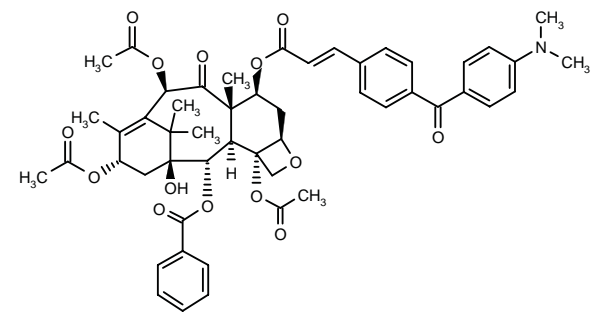
REFERENCES

1. Wang, S. et al. *Studies on quinazolinones as dual inhibitors of Pgp and MRP1 in multidrug resistance*. *Bioorg Med Chem Lett* 2002, 12(4): 571.

tRA-98006

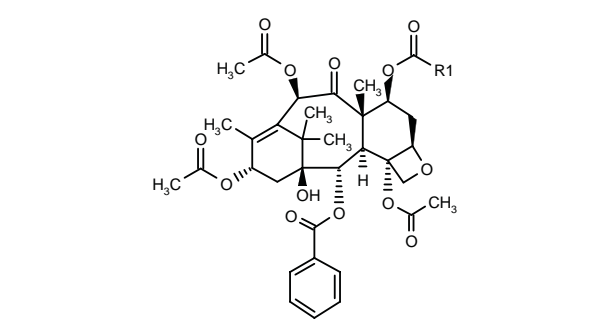
318242

(2a*R*,4*S*,4a*S*,6*R*,9*S*,11*S*,12*S*,12a*R*,12b*S*)-6,9,12b-Tris(acetoxy)-12-(benzoyloxy)-4-[3-[4-(4-dimethyl-amino)benzoyl]phenyl]-2(*E*)-propenoyloxy]-11-hydroxy-4a,8,13,13-tetramethyl-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-1*H*-7,11-methanocyclodeca[3,4]benzo-[1,2-*b*]oxet-5-one



C51 H55 N O14; Mol wt: 905.9885

ACTION – Noncytotoxic multidrug resistance (MDR) modulator with a taxane backbone, proven to modulate P-glycoprotein (Pgp)-, multidrug resistance protein (MRP1)- and/or breast cancer resistance protein (BCRP)-mediated drug efflux. Compound strongly enhanced the retention and cytotoxic effect of mitoxantrone in Pgp-, MRP1- and BCRP-expressing tumor cell lines at the noncytotoxic concentration of 1 µM. Potentially useful for combination chemotherapy. Other related compounds are:



Compound	R1	Formula
tRA-99020 [318244]	4-(PhCO)-Ph	C ₄₇ H ₄₈ O ₁₄
tRA-99037 [318245]	2-Naph-OCH2	C ₄₈ H ₄₈ O ₁₄

SOURCES – Roswell Park Cancer Institute, Buffalo, NY (US); State University of New York, Stony Brook, NY (US).

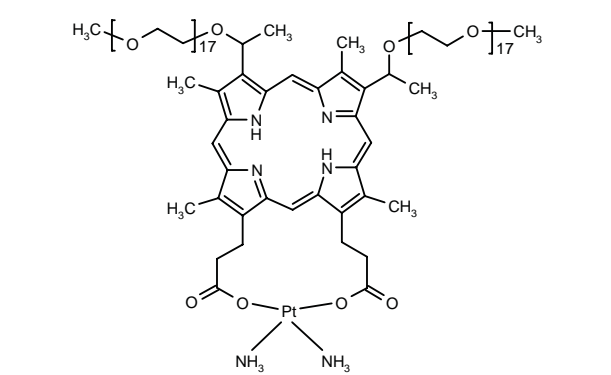
REFERENCES

1. Brooks, T.A. et al. *Modulatory ability and structure relationships of taxane reversal agents (tRAs) against P-glycoprotein (Pgp)-, multidrug resistance protein (MRP-1)-, and breast cancer resistance protein (BCRP)- mediated mitoxantrone transport.* Proc Am Assoc Cancer Res 2002, 43: Abst 4725.

RADIATION THERAPY

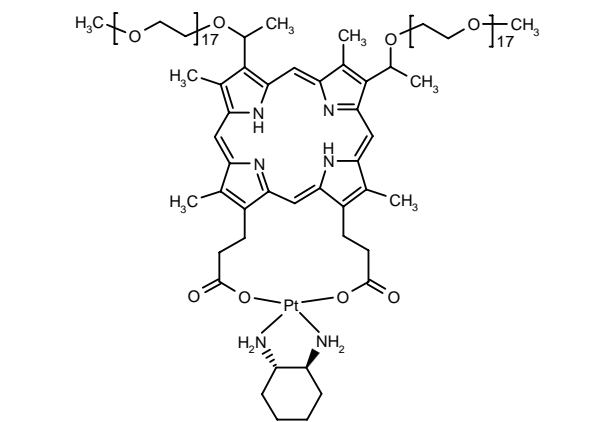
319013

Diammine[7,13-bis[1-(methoxypolyethyleneglycol-750)-ethyl]-3,8,12,17-tetramethyl-21*H*,23*H*-porphyrin-2,18-dipropionato]platinum



C104 H182 N6 O40 Pt; Mol wt: 2351.6640

ACTION – Porphyrin–platinum conjugate with combined cytotoxic and phototoxic antitumor activity in bladder cancer TCC-SUP and J82 cell lines. In the dark, the cytotoxicity of compound was higher than cisplatin and after irradiation its cytotoxicity increased dramatically and exceeded the sum of the phototoxicity of the corresponding porphyrin ligand and the cytotoxicity of cisplatin. Another related compound is:



319015: C110 H190 N6 O40 Pt

SOURCE – Universität Regensburg, Regensburg (DE).

REFERENCES

1. Lottner, C. et al. *Hematoporphyrin-derived soluble porphyrin-platinum conjugates with combined cytotoxic and phototoxic antitumor activity.* J Med Chem 2002, 45(10): 2064.

CHEMOPROTECTIVE AGENTS

CTCE-0021¹⁻³

319001

L-Lysyl-L-prolyl-L-valyl-L-seryl-L-leucyl-L-seryl-L-tyrosyl-L-arginyl-L-cysteinyl-L-prolyl-L-cysteinyl-L-arginyl-L-phenylalanyl-L-phenylalanyl-glycyl-glycyl-glycyl-L-leucyl-L-lysyl-L-tryptophyl-L-isoleucyl-L-glutamyl-L-glutamyl-L-tyrosyl-L-leucyl-L-glutamyl-L-lysyl-L-alanyl-L-leucyl-L-asparaginamide N-6.20-C-5.24-lactam

C164 H250 N44 O40 S2; Mol wt: 3542.1790

ACTION – Small peptide analogue of stromal cell-derived factor 1 (SDF-1, CLCL12) with slightly lower affinity for the SDF-1 receptor compared to native SDF-1 (CXCR4; IC₅₀ = 226 and 36.6 nM, respectively). Compound also induced maximal calcium mobilization in THP-1 cells (IC₅₀ = 147.9 nM) and was as effective as native SDF-1 in repressing BFU-E (erythroid precursor) and CFU-GM (granulocyte–monocyte precursor) cells. Potentially useful for protecting hematopoietic stem cells during peripheral blood progenitor cell collection and bone marrow harvesting associated with myelosuppressive therapies. Another related compound is:

L-Lysyl-L-prolyl-L-valyl-L-seryl-L-leucyl-L-seryl-L-tyrosyl-L-arginyl-L-cysteinyl-L-prolyl-L-cysteinyl-L-arginyl-L-phenylalanyl-L-phenylalanyl-glycyl-glycyl-glycyl-L-leucyl-L-lysyl-L-tryptophyl-L-isoleucyl-L-glutamyl-L-glutamyl-L-tyrosyl-L-leucyl-L-glutamyl-L-lysyl-L-alanyl-L-leucyl-L-asparaginamide N-6.28-C-5.24-lactam

CTCE-0022 [319002]^{1,2}: C164 H250 N44 O40 S2

SOURCES – University of British Columbia, Vancouver, BC (CA); Chemokine Therapeutics.

REFERENCES

1. Salari, H. et al. (Chemokine Therapeutics Corp.) *CXCR4* agonist treatment of hematopoietic cells. WO 0176615.

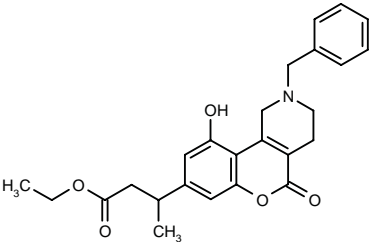
2. Tudan, C. et al. C-Terminal cyclization of an SDF-1 small peptide analogue dramatically increases receptor affinity and activation of the CXCR4 receptor. *J Med Chem* 2002, 45(10): 2024.

3. *Company Profile: Chemokine Therapeutics*. DailyDrugNews.com (Daily Essentials) 2001, May 23.

OCULAR MEDICATIONS

318446

3-(2-Benzyl-10-hydroxy-5-oxo-2,3,4,5-tetrahydro-1*H*-1-benzopyran[4,3-*c*]pyridin-8-yl)butyric acid ethyl ester



C25 H27 N O5; Mol wt: 421.4903

ACTION – Cannabinoid analogue designed on the basis of a soft drug design approach, with local intraocular pressure (IOP)-lowering activity and minimal or no systemic activity due to its rapid inactivation. In rabbits it displayed significant and short-lasting (15 min) reductions in IOP following i.v. administration at a dose of 1 mg/kg, with a maximum decrease of 18%, and long-lasting IOP-lowering activity after topical administration of a 1% solution. Its metabolite demonstrated virtually no activity following i.v. dosing. Potentially useful for the treatment of glaucoma.

SOURCES – University of Florida, Gainesville, FL (US); Kos Pharmaceuticals.

REFERENCES

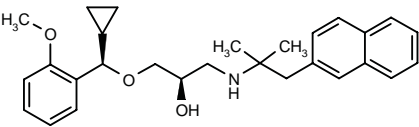
1. Buchwald, A. et al. *Soft cannabinoid analogues as potential anti-glaucoma agents*. *Pharmazie* 2002, 57(2): 108.

METABOLIC DRUGS

TREATMENT OF BONE DISEASES

317902

1-[1(*R*)-Cyclopropyl-1-(2-methoxyphenyl)methoxy]-3-[1,1-dimethyl-2-(2-naphthyl)ethylamino]propan-2(*R*)-ol



C28 H35 N O3; Mol wt: 433.5885

CHEMOPROTECTIVE AGENTS

CTCE-0021¹⁻³

319001

L-Lysyl-L-prolyl-L-valyl-L-seryl-L-leucyl-L-seryl-L-tyrosyl-L-arginyl-L-cysteinyl-L-prolyl-L-cysteinyl-L-arginyl-L-phenylalanyl-L-phenylalanyl-glycyl-glycyl-glycyl-L-leucyl-L-lysyl-L-tryptophyl-L-isoleucyl-L-glutamyl-L-glutamyl-L-tyrosyl-L-leucyl-L-glutamyl-L-lysyl-L-alanyl-L-leucyl-L-asparaginamide *N*-6.20-C-5.24-lactam

C164 H250 N44 O40 S2; Mol wt: 3542.1790

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L-Lysyl-L-prolyl-L-valyl-L-seryl-L-leucyl-L-seryl-L-tyrosyl-L-arginyl-L-cysteinyl-L-prolyl-L-cysteinyl-L-arginyl-L-phenylalanyl-L-phenylalanyl-glycyl-glycyl-glycyl-L-leucyl-L-lysyl-L-tryptophyl-L-isoleucyl-L-glutamyl-L-glutamyl-L-tyrosyl-L-leucyl-L-glutamyl-L-lysyl-L-alanyl-L-leucyl-L-asparaginamide *N*-6.28-C-5.24-lactam

CTCE-0022 [319002]^{1,2}: C164 H250 N44 O40 S2

SOURCES – University of British Columbia, Vancouver, BC (CA); Chemokine Therapeutics.

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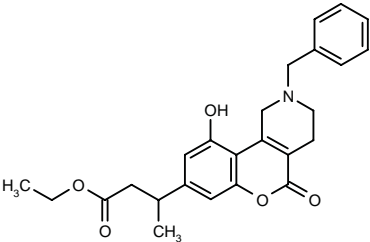
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3. *Company Profile: Chemokine Therapeutics*. DailyDrugNews.com (Daily Essentials) 2001, May 23.

OCULAR MEDICATIONS

318446

3-(2-Benzyl-10-hydroxy-5-oxo-2,3,4,5-tetrahydro-1*H*-1-benzopyran[4,3-*c*]pyridin-8-yl)butyric acid ethyl ester



C25 H27 N O5; Mol wt: 421.4903

ACTION – Cannabinoid analogue designed on the basis of a soft drug design approach, with local intraocular pressure (IOP)-lowering activity and minimal or no systemic activity due to its rapid inactivation. In rabbits it displayed significant and short-lasting (15 min) reductions in IOP following i.v. administration at a dose of 1 mg/kg, with a maximum decrease of 18%, and long-lasting IOP-lowering activity after topical administration of a 1% solution. Its metabolite demonstrated virtually no activity following i.v. dosing. Potentially useful for the treatment of glaucoma.

SOURCES – University of Florida, Gainesville, FL (US); Kos Pharmaceuticals.

REFERENCES

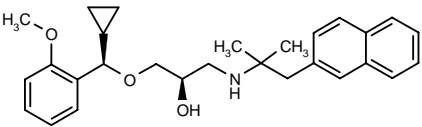
1. Buchwald, A. et al. *Soft cannabinoid analogues as potential anti-glaucoma agents*. Pharmazie 2002, 57(2): 108.

METABOLIC DRUGS

TREATMENT OF BONE DISEASES

317902

1-[1(*R*)-Cyclopropyl-1-(2-methoxyphenyl)methoxy]-3-[1,1-dimethyl-2-(2-naphthyl)ethylamino]propan-2(*R*)-ol



C28 H35 N O3; Mol wt: 433.5885

CHEMOPROTECTIVE AGENTS

CTCE-0021¹⁻³

319001

L-Lysyl-L-prolyl-L-valyl-L-seryl-L-leucyl-L-seryl-L-tyrosyl-L-arginyl-L-cysteinyl-L-prolyl-L-cysteinyl-L-arginyl-L-phenylalanyl-L-phenylalanyl-glycyl-glycyl-glycyl-L-leucyl-L-lysyl-L-tryptophyl-L-isoleucyl-L-glutamyl-L-glutamyl-L-tyrosyl-L-leucyl-L-glutamyl-L-lysyl-L-alanyl-L-leucyl-L-asparaginamide N-6.20-C-5.24-lactam

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ACTION – Small peptide analogue of stromal cell-derived factor 1 (SDF-1, CLCL12) with slightly lower affinity for the SDF-1 receptor compared to native SDF-1 (CXCR4; IC₅₀ = 226 and 36.6 nM, respectively). Compound also induced maximal calcium mobilization in THP-1 cells (IC₅₀ = 147.9 nM) and was as effective as native SDF-1 in repressing BFU-E (erythroid precursor) and CFU-GM (granulocyte-monocyte precursor) cells. Potentially useful for protecting hematopoietic stem cells during peripheral blood progenitor cell collection and bone marrow harvesting associated with myelosuppressive therapies. Another related compound is:

L-Lysyl-L-prolyl-L-valyl-L-seryl-L-leucyl-L-seryl-L-tyrosyl-L-arginyl-L-cysteinyl-L-prolyl-L-cysteinyl-L-arginyl-L-phenylalanyl-L-phenylalanyl-glycyl-glycyl-glycyl-L-leucyl-L-lysyl-L-tryptophyl-L-isoleucyl-L-glutamyl-L-glutamyl-L-tyrosyl-L-leucyl-L-glutamyl-L-lysyl-L-alanyl-L-leucyl-L-asparaginamide N-6.28-C-5.24-lactam

CTCE-0022 [319002]^{1,2}: C164 H250 N44 O40 S2

SOURCES – University of British Columbia, Vancouver, BC (CA); Chemokine Therapeutics.

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1. Salari, H. et al. (Chemokine Therapeutics Corp.) *CXCR4* agonist treatment of hematopoietic cells. WO 0176615.

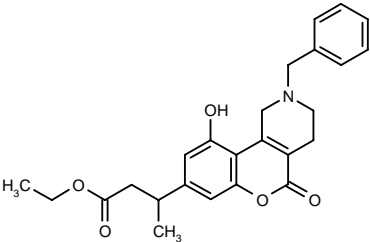
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OCULAR MEDICATIONS

318446

3-(2-Benzyl-10-hydroxy-5-oxo-2,3,4,5-tetrahydro-1*H*-1-benzopyran[4,3-*c*]pyridin-8-yl)butyric acid ethyl ester



C25 H27 N O5; Mol wt: 421.4903

ACTION – Cannabinoid analogue designed on the basis of a soft drug design approach, with local intraocular pressure (IOP)-lowering activity and minimal or no systemic activity due to its rapid inactivation. In rabbits it displayed significant and short-lasting (15 min) reductions in IOP following i.v. administration at a dose of 1 mg/kg, with a maximum decrease of 18%, and long-lasting IOP-lowering activity after topical administration of a 1% solution. Its metabolite demonstrated virtually no activity following i.v. dosing. Potentially useful for the treatment of glaucoma.

SOURCES – University of Florida, Gainesville, FL (US); Kos Pharmaceuticals.

REFERENCES

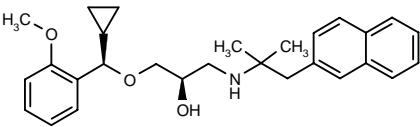
1. Buchwald, A. et al. *Soft cannabinoid analogues as potential anti-glaucoma agents*. Pharmazie 2002, 57(2): 108.

METABOLIC DRUGS

TREATMENT OF BONE DISEASES

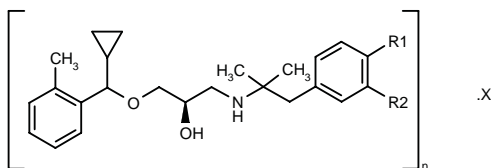
317902

1-[1(*R*)-Cyclopropyl-1-(2-methoxyphenyl)methoxy]-3-[1,1-dimethyl-2-(2-naphthyl)ethylamino]propan-2(*R*)-ol



C28 H35 N O3; Mol wt: 433.5885

ACTION – Calcium receptor antagonist that gave an IC_{50} of 0.022 μM against human calcium receptors expressed in rat adrenal cells. Compound was shown to increase serum parathyroid hormone (PTH) concentrations following oral administration to rats at a dose of 30 mg/kg. Potentially useful for the treatment of disorders associated with abnormal calcium homeostasis, particularly osteoporosis. Other applications include hypoparathyroidism, osteosarcoma, periodontitis, bone fracture, osteoarthritis, chronic rheumatoid arthritis, Paget's disease and humoral and autosomal dominant hypercalcemia. Other exemplified compounds are:



Compound	R1	R2	n	X	Isomer	Formula
317903	-CH=CHCH=CH-		1			C ₂₈ H ₃₅ NO ₂
317904	-CH=CHCH=CH-		1		R	C ₂₈ H ₃₅ NO ₂
317905	OMe	Me	2	fumarate	R	C ₅₆ H ₇₈ N ₂ O ₁₀
317906	Me	Me	2	fumarate	R	C ₅₆ H ₇₈ N ₂ O ₈

SOURCE – Japan Tobacco.

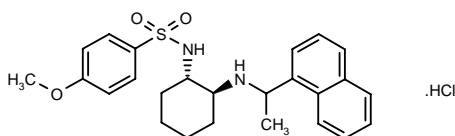
REFERENCES

1. Shinagawa, Y. et al. (Japan Tobacco Inc.) *Calcium receptor antagonists*. WO 0214259.

PHD-263

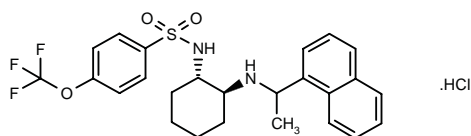
317272

4-Methoxy-*N*-[(1*S*,2*S*)-2-[1-(1-naphthyl)ethylamino]-cyclohexyl]benzenesulfonamide hydrochloride



C₂₅ H₃₀ N₂ O₃ S . HCl; Mol wt: 475.0499

ACTION – Calcium-sensing receptor (CaSR) antagonist shown to inhibit extracellular calcium-induced accumulation of inositol phosphates in CHO cells by 64% at 10 μ M. Potentially useful for the treatment of disorders associated with calcium imbalance including hyperparathyroidism, osteoporosis, Paget's disease, rheumatoid arthritis, osteoarthritis, osteosarcoma, bone fractures and cancer, as well as cardiovascular, gastrointestinal, endocrine and neurodegenerative diseases. Another exemplified diamine is:



PHD-401 [317273]: C25 H27 F3 N2 O3 S . HCl

SOURCE – CNRS.

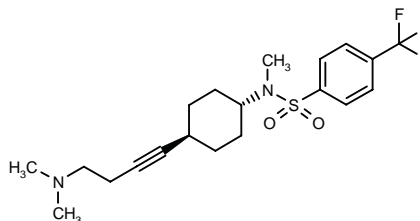
REFERENCES

1. Dauban, P.M. et al. (CNRS [Centre National de la Recherche Scientifique]) *Novel diamines having a CaSR modulating activity*. FR 2812875, WO 0212181.

TREATMENT OF LIPOPROTEIN DISORDERS

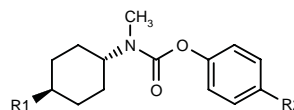
317517

trans-*N*-[4-[4-(Dimethylamino)-1-butynyl]cyclohexyl]-*N*-methyl-4-(trifluoromethyl)benzenesulfonamide

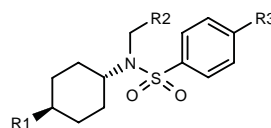


C20 H27 F3 N2 O2 S; Mol wt: 416.5053

ACTION – An inhibitor of 2,3-epoxysqualene-lanosterol cyclase (lanosterol synthase) with potential in the treatment of hypercholesterolemia, hyperlipidemia, arteriosclerosis and other vascular diseases, mycoses, parasite infections, gallstones, proliferative disorders including cancer, impaired glucose tolerance and diabetes. Other specifically claimed cyclohexylamino derivatives include the following:



Compound	R1	R2	Formula
317518	5-(MeNH)-pentyl	CF ₃	C ₂₁ H ₂₉ F ₃ N ₂ O ₂
317523	PrN(Me)CH ₂ -ethynyl	Cl	C ₂₁ H ₂₉ ClN ₂ O ₂



Compound	R1	R2	R3	Formula
317519	O(CH ₂) ₄ N(Me)CH ₂ CH ₂ OH	Me	CF ₃	C ₂₂ H ₃₆ F ₃ N ₂ O ₄ S
317520	OCH ₂ CH ₂ N(i-Pr) ₂	H	Br	C ₂₁ H ₃₆ BrN ₂ O ₃ S
317521	1-Pip-(CH ₂) ₄	H	CF ₃	C ₂₃ H ₃₆ F ₃ N ₂ O ₂ S
317522	1-Pip-CH ₂ CH ₂ O	H	Br	C ₂₀ H ₃₁ BrN ₂ O ₃ S
317524	EtN(CH ₂ CH ₂ OH)CH ₂ CH ₂ -ethynyl	H	CF ₃	C ₂₂ H ₃₁ F ₃ N ₂ O ₃ S
317525	1-N(Me) ₂ -2-cyclopropyl-CH ₂ CH ₂ O	H	CF ₃	C ₂₁ H ₃₁ F ₃ N ₂ O ₃ S

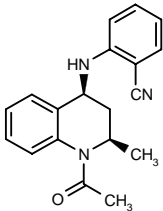
SOURCE – Roche.

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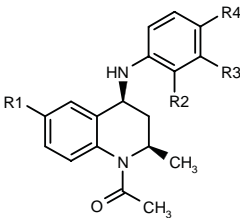
317686

2-[1-Acetyl-2(*R*)-methyl-1,2,3,4-tetrahydroquinolin-4(*S*)-ylamino]benzonitrile



C19 H19 N3 O; Mol wt: 305.3791

ACTION – Agent with the ability to stimulate the production of apolipoprotein A-I (apo A-I), potentially useful for the treatment of hyperlipidemia and arteriosclerosis. Compound was shown to increase the production of apo A-I in HepG2 cells by 10, 24 and 49%, respectively, compared to controls at 1, 3 and 10 μM. *In vivo*, it induced an increase of 80 and 73%, respectively, in blood levels of apo A-I and HDL cholesterol following oral administration to rats at 30 mg/kg/day for 7 days. Other exemplified 1,2,3,4-tetrahydroquinoline derivatives are:



Compound	R1	R2	R3	R4	Formula
317687	OMe	H	H	OMe	C ₂₀ H ₂₄ N ₂ O ₃
317689	H	H	H	OMe	C ₁₉ H ₂₂ N ₂ O ₂
317692	H	H	H	Cl	C ₁₈ H ₁₉ ClN ₂ O
317694	H	OMe	H	H	C ₁₉ H ₂₂ N ₂ O ₂
317696	H	H	Me	H	C ₁₈ H ₂₂ N ₂ O

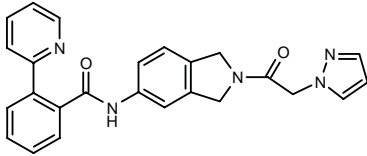
SOURCE – Japan Tobacco.

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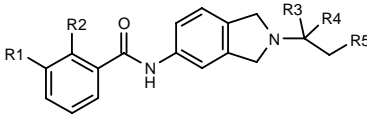
317852

N-[2-[2-(1*H*-Pyrazol-1-yl)acetyl]-2,3-dihydro-1*H*-isoindol-5-yl]-2-(2-pyridyl)benzamide



C25 H21 N5 O2; Mol wt: 423.4739

ACTION – Agent with the ability to inhibit the secretion of apolipoprotein B (apo B) and reduce serum lipids. By virtue of its activity, this compound is considered to have potential in the treatment of hyperlipidemia, ischemic cardiopathy, atherosclerosis, coronary arteriosclerosis, hypercholesterolemia, hypertriglyceridemia, hyperlipoproteinemia, coronary cardiopathy, ischemic encephalopathy, stroke, circulation and microcirculation disorders, thrombosis, hyperglycemia, diabetes, acute hemorrhagic pancreatitis, obesity, constipation, etc. Other exemplified benzoylaminoisoindole compounds are:



Compound	R1	R2	R3	R4	R5	Formula
317853	H	3-thienyl	-O-		1-pyrazolyl	C ₂₄ H ₂₀ N ₄ O ₂ S
317854	CO ₂ Me	5-CF ₃ -2-Pyr	-O-		1-pyrazolyl	C ₂₈ H ₂₂ F ₃ N ₅ O ₄
317855	H	2-pyrimidinyl	-O-		1-pyrazolyl	C ₂₄ H ₂₀ N ₆ O ₂
317856	H	5-Ac-2-Pyr	-O-		1-pyrazolyl	C ₂₇ H ₂₃ N ₅ O ₃
317857	H	5-Ac-2-Pyr	H	H	1-pyrazolyl	C ₂₇ H ₂₅ N ₅ O ₂
317858	H	5-CF ₃ -2-Pyr	-O-		2-Pyr	C ₂₈ H ₂₁ F ₃ N ₄ O ₂
317859	H	5-CF ₃ -2-Pyr	-O-		3-thienyl	C ₂₇ H ₂₀ F ₃ N ₅ O ₂ S
317860	H	5-CF ₃ -2-Pyr	-O-		4-(CO ₂ Et)-1-pyrazolyl	C ₂₉ H ₂₄ F ₃ N ₅ O ₄

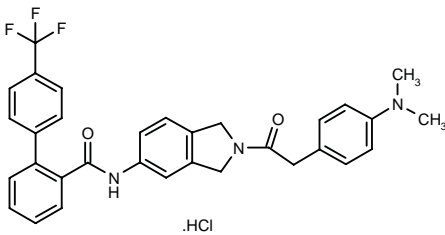
SOURCE – Tanabe Seiyaku.

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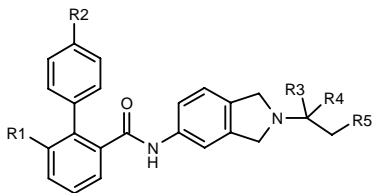
317861

N-[2-[2-[4-(Dimethylamino)phenyl]acetyl]-2,3-dihydro-1*H*-isoindol-5-yl]-4'-(trifluoromethyl)biphenyl-2-carboxamide hydrochloride



C32 H28 F3 N3 O2 . HCl; Mol wt: 580.0471

ACTION – Agent with the ability to inhibit the secretion of apolipoprotein B (apo B) and reduce serum lipids. By virtue of its activity, this compound is considered to have potential in the treatment of hyperlipidemia, ischemic cardiopathy, atherosclerosis, coronary arteriosclerosis, hypercholesterolemia, hypertriglyceridemia, hyperlipoproteinemia, coronary cardiopathy, ischemic encephalopathy, stroke, circulation and microcirculation disorders, thrombosis, hyperglycemia, diabetes, acute hemorrhagic pancreatitis, obesity, constipation, etc. Other exemplified biphenylcarboxamidoisindoline compounds are:



Compound	R1	R2	R3	R4	R5	Formula
317862	H	CF3	-O-		1-Me-2-pyrrolyl	C ₂₉ H ₂₄ F ₃ N ₃ O ₂
317863	H	CF3	-O-		1-imidazolyl	C ₂₇ H ₂₁ F ₃ N ₄ O ₂
317864	OCH2CH2OMe	CF3	-O-		3-NH2-4-CN-1-pyrazolyl	C ₃₂ H ₂₇ F ₃ N ₆ O ₄
317865	H	OCH2OMe	-O-		1-pyrazolyl	C ₂₈ H ₂₆ N ₄ O ₄
317866	H	CON(Me)-CH2CH2Ph	-O-		1-pyrazolyl	C ₃₆ H ₃₃ N ₅ O ₃
317867	H	OCH2CH2-N(Me)2	-O-		1-pyrazolyl	C ₃₀ H ₃₁ N ₅ O ₃
317868	OC(Me)2-CO2Me	CF3	-O-		1-pyrazolyl	C ₃₂ H ₂₉ F ₃ N ₄ O ₅
317869	H	CF3	H	H	2-thienyl	C ₂₈ H ₂₃ F ₃ N ₂ OS

SOURCE – Tanabe Seiyaku.

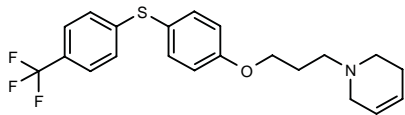
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TREATMENT OF OBESITY
AND NUTRITIONAL DISORDERS

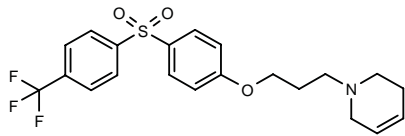
317621

1-[3-[4-[4-(Trifluoromethyl)phenylsulfanyl]phenoxy]propyl]-1,2,3,6-tetrahydropyridine



C21 H22 F3 N O S; Mol wt: 393.4708

ACTION – Agent for the prevention and treatment of obesity and diabetes. *In vivo*, this compound was shown to induce a 27% decrease in body weight, and also reduced by 77 and 92%, respectively, plasma levels of glucose and insulin following s.c. administration to mice at a dose of 80 mg/kg. Another exemplified cyclic amine derivative is:



317620: C21 H22 F3 N O3 S

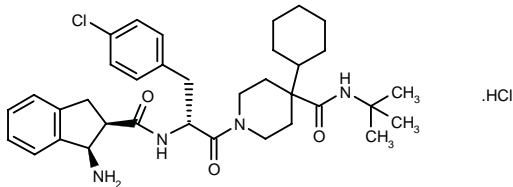
SOURCE – Shionogi.

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318013

cis-1-[*N*-(1-Amino-2,3-dihydro-1*H*-inden-2-ylcarbonyl)-4-chloro-*D*-phenylalanyl]-*N*-*tert*-butyl-4-cyclohexylpiperidine-4-carboxamide hydrochloride



C35 H47 Cl N4 O3 . HCl; Mol wt: 643.6952

ACTION – A representative compound from a series of substituted piperidine derivatives that acts as a selective melanocortin MC₄ receptor agonist. As such, this compound is expected to be useful for the treatment of obesity, diabetes and male and female sexual dysfunction.

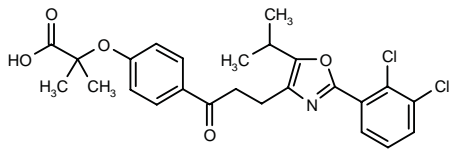
SOURCE – Merck & Co.

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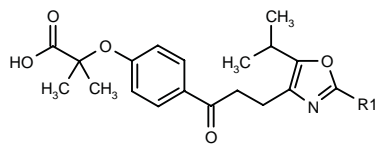
318026

2-[4-[3-[2-(2,3-Dichlorophenyl)-5-isopropoxyoxazol-4-yl]propionyl]phenoxy]-2-methylpropionic acid



C25 H25 Cl2 N O5; Mol wt: 490.3805

ACTION – Agent with the ability to activate peroxisome proliferator-activated PPAR δ receptors, proven to increase the activity of PPAR δ receptors in monkey renal fibroblast CV-1 cells by 96 \pm 13% at 10 μ M compared to 8 and 19% activation of PPAR α and PPAR γ receptors, respectively. Potentially useful for the treatment of obesity, syndrome X, hypercholesterol-emia and hyperlipidemia, arteriosclerosis, ischemic diseases, cancer, Alzheimer's disease, inflammation, osteoporosis, thyrotoxic ophthalmopathy and adreno-leukodystrophy. Other exemplified compounds are:



Compound	R1	Formula
318029	1-OH-2-Naph	C ₂₅ H ₂₉ NO ₆
318030	4-Cl-2-OH-Ph	C ₂₅ H ₂₆ ClNO ₆
318031	4-Br-2-Cl-Ph	C ₂₅ H ₂₅ BrClNO ₅

SOURCE – Nippon Chemiphar.

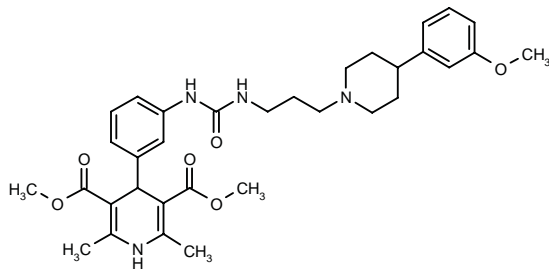
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BMS-193885

247163

4-[3-[3-[3-[4-(3-Methoxyphenyl)piperidin-1-yl]propyl]-ureido]phenyl]-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylic acid dimethyl ester



C33 H42 N4 O6; Mol wt: 590.7168

ACTION – Neuropeptide Y (NPY) Y₁ receptor antagonist with high selectivity for Y₁ (K_i = 3.3 nM) over Y₂, Y₄ and Y₅ receptors (K_i > 1000 nM); it showed competitive antagonism of NPY-mediated inhibition of forskolin-stimulated cAMP accumulation in CHO cells expressing the human Y₁ receptor (K_b = 4.5 nM). *In vivo*, it dose-dependently antagonized NPY-induced feeding in satiated rats (33 and 57% reduction at 10 and 30 mg/kg i.p., respectively) and it also inhibited spontaneous nocturnal food intake in rats. Potentially useful for the treatment of hyperphagia and obesity.

SOURCE – Bristol-Myers Squibb.

REFERENCES

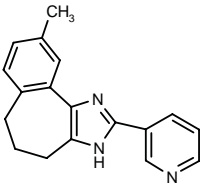
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FR-252384

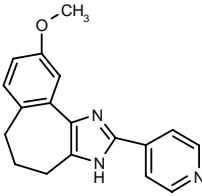
311289

9-Methyl-2-(3-pyridyl)-3,4,5,6-tetrahydrobenzo[3,4]-cyclohepta[1,2-*d*]imidazole



C18 H17 N3; Mol wt: 275.3533

ACTION – Potent neuropeptide Y (NPY) Y₅ receptor antagonist with nanomolar affinity for the human Y₅ receptor (IC₅₀ = 2.3 nM) and good oral absorption and penetration into the brain in Zucker fatty rats. Potentially useful for the treatment of obesity. Another related compound is:



FR-240662 [311287]: C18 H17 N3 O

SOURCE – Fujisawa.

REFERENCES

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HEMATINIC AGENTS AND
HEMATOPOIETIC GROWTH FACTORS

PEGFILGRASTIM

279036

Covalent conjugate of recombinant methionyl human G-CSF (filgrastim) and monomethoxypolyethylene glycol (PEG) produced by the covalent binding of a 20-kD PEG molecule to the N-terminal methionyl residue of filgrastim, with an average molecular weight of approximately 39 kD

Filgrastim SD-01
PEG-filgrastim
Pegylated filgrastim
SD-01
SD/01

ACTION – Covalent conjugate of recombinant methionyl human granulocyte colony-stimulating factor (G-CSF, filgrastim) and monomethoxypolyethylene glycol. It binds to specific cell-surface receptors of hematopoietic cells, thereby stimulating proliferation, differentiation, commitment and functional activation.

INDICATION – For decreasing the incidence of infection, manifested as febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anticancer drugs.

PRESENTATION – Prefilled syringe for s.c. injection, containing 6 mg pegfilgrastim (based on protein weight) in 0.6 ml.

PROPRIETARY NAME – Neulasta (US).

SOURCE – Amgen.

REFERENCES

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6. George, S. et al. *Pharmacokinetic profiles of fixed dose single pegfilgrastim administration in patients with non-Hodgkin's lymphoma.* Blood 2001, 98(11, Part 2): Abst 3700.

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9. Holmes, F.A. et al. *A single dose of Peg-filgrastim is as effective as daily filgrastim to reduce the duration of severe, chemotherapy-induced neutropenia.* Proc Am Soc Clin Oncol 2000, 19: Abst 191.

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14. McKenna, P.J. et al. *Filgrastim-SD, a sustained duration form of filgrastim. (rhuG-CSF) has similar effects on neutrophil function compared to filgrastim.* Blood 1998, 92(10, Suppl. 1, Part 1): Abst 1562.

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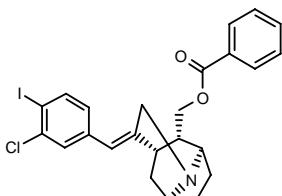
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TREATMENT OF POISONING, DRUG ABUSE AND DEPENDENCY

318681

Benzoic acid [(3*S*,6*Z*,7*S*,8*S*,8*aR*)-6-(3-chloro-4-iodobenzylidene)perhydro-3,7-methanoindolizin-8-yl]methyl ester



C₂₄ H₂₃ Cl I N O₂; Mol wt: 519.8037

ACTION – Potent and selective 5-HT transporter (SERT) inhibitor ($K_i = 0.06$ nM) inactive against dopamine and noradrenaline transporters at up to 10 μ M. Potentially useful for the treatment of cocaine abuse.

SOURCES – Georgetown University, Washington, DC (US); University of Texas Medical Branch at Galveston, Galveston, TX (US).

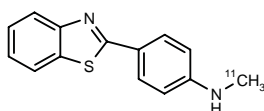
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DIAGNOSTIC AGENTS

317360

N-[4-(2-Benzothiazolyl)phenyl]-*N*-[¹¹C]-methylamine



C₁₄ H₁₂ N₂ S; Mol wt: 239.3178

ACTION – Lipophilic thioflavin-T derivative for positron emission tomography (PET) imaging of amyloid deposition in Alzheimer's disease. *In vitro* tests showed high affinity for A β (1-40) fibrils ($K_i = 11$ nM) and uptake experiments in mice showed high brain uptake and rapid clearance after i.v. administration. Unlabeled compound injected into transgenic PS1/APP mice resulted in visualization of both cerebral plaques and cerebrovascular amyloid deposits.

SOURCE – University of Pittsburgh, Pittsburgh, PA (US).

REFERENCES

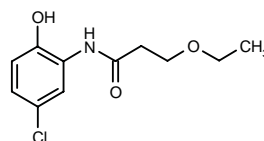
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2. Mathis, C.A. et al. *A lipophilic thioflavin-T derivative for positron emission tomography (PET) imaging of amyloid in brain.* Bioorg Med Chem Lett 2002, 12(3): 295.

DRUG DELIVERY

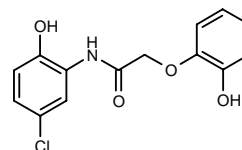
318011

N-(5-Chloro-2-hydroxyphenyl)-3-ethoxypropionamide



C₁₁ H₁₄ Cl N O₃; Mol wt: 243.6886

ACTION – Carrier compound useful for delivering active agents such as proteins, peptides, polysaccharides, mucopolysaccharides and lipids by different routes including oral administration. This compound demonstrated efficacy in the delivery of salmon calcitonin to rats following oral administration. Another exemplified compound is:



318012: C₁₄ H₁₂ Cl N O₄

SOURCE – Emisphere Technologies.

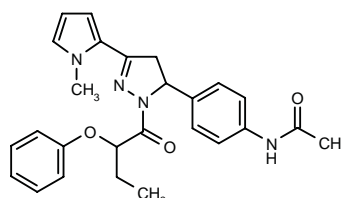
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PHARMACOLOGICAL TOOLS

318270

N-[4-[3-(1-Methyl-1*H*-pyrrol-2-yl)-1-(2-phenoxybutyryl)-4,5-dihydro-1*H*-pyrazol-5-yl]phenyl]acetamide

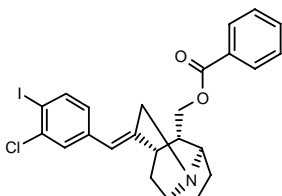


C₂₆ H₂₈ N₄ O₃; Mol wt: 444.5322

TREATMENT OF POISONING, DRUG ABUSE AND DEPENDENCY

318681

Benzoic acid [(3*S*,6*Z*,7*S*,8*S*,8*aR*)-6-(3-chloro-4-iodobenzylidene)perhydro-3,7-methanoindolizin-8-yl]methyl ester



C₂₄ H₂₃ Cl I N O₂; Mol wt: 519.8037

ACTION – Potent and selective 5-HT transporter (SERT) inhibitor ($K_i = 0.06$ nM) inactive against dopamine and noradrenaline transporters at up to 10 μ M. Potentially useful for the treatment of cocaine abuse.

SOURCES – Georgetown University, Washington, DC (US); University of Texas Medical Branch at Galveston, Galveston, TX (US).

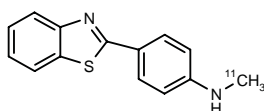
REFERENCES

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DIAGNOSTIC AGENTS

317360

N-[4-(2-Benzothiazolyl)phenyl]-*N*-[¹¹C]-methylamine



C₁₄ H₁₂ N₂ S; Mol wt: 239.3178

ACTION – Lipophilic thioflavin-T derivative for positron emission tomography (PET) imaging of amyloid deposition in Alzheimer's disease. *In vitro* tests showed high affinity for A β (1-40) fibrils ($K_i = 11$ nM) and uptake experiments in mice showed high brain uptake and rapid clearance after i.v. administration. Unlabeled compound injected into transgenic PS1/APP mice resulted in visualization of both cerebral plaques and cerebrovascular amyloid deposits.

SOURCE – University of Pittsburgh, Pittsburgh, PA (US).

REFERENCES

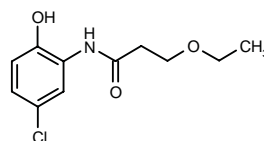
1. Klunk, W.E. et al. (University of Pittsburgh) *Thioflavin derivs. for use in antemortem diagnosis of Alzheimer's disease and in vivo imaging and prevention of amyloid deposition.* WO 0216333.

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DRUG DELIVERY

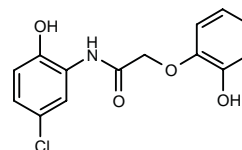
318011

N-(5-Chloro-2-hydroxyphenyl)-3-ethoxypropionamide



C₁₁ H₁₄ Cl N O₃; Mol wt: 243.6886

ACTION – Carrier compound useful for delivering active agents such as proteins, peptides, polysaccharides, mucopolysaccharides and lipids by different routes including oral administration. This compound demonstrated efficacy in the delivery of salmon calcitonin to rats following oral administration. Another exemplified compound is:



318012: C₁₄ H₁₂ Cl N O₄

SOURCE – Emisphere Technologies.

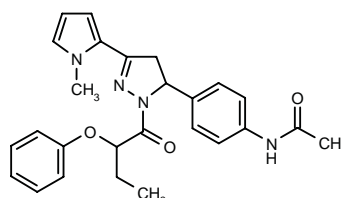
REFERENCES

1. Tang, P. (Emisphere Technologies, Inc.) *Cpds. and compsns. for delivering active agents.* WO 0216309.

PHARMACOLOGICAL TOOLS

318270

N-[4-[3-(1-Methyl-1*H*-pyrrol-2-yl)-1-(2-phenoxybutyryl)-4,5-dihydro-1*H*-pyrazol-5-yl]phenyl]acetamide

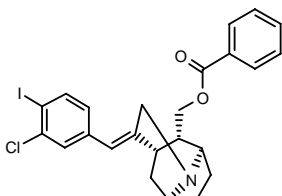


C₂₆ H₂₈ N₄ O₃; Mol wt: 444.5322

TREATMENT OF POISONING, DRUG ABUSE AND DEPENDENCY

318681

Benzoic acid [(3*S*,6*Z*,7*S*,8*S*,8*aR*)-6-(3-chloro-4-iodobenzylidene)perhydro-3,7-methanoindolizin-8-yl]methyl ester



C₂₄ H₂₃ Cl I N O₂; Mol wt: 519.8037

ACTION – Potent and selective 5-HT transporter (SERT) inhibitor ($K_i = 0.06$ nM) inactive against dopamine and noradrenaline transporters at up to 10 μ M. Potentially useful for the treatment of cocaine abuse.

SOURCES – Georgetown University, Washington, DC (US); University of Texas Medical Branch at Galveston, Galveston, TX (US).

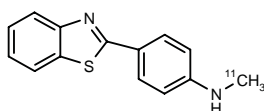
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SOURCE – University of Pittsburgh, Pittsburgh, PA (US).

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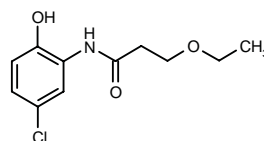
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DRUG DELIVERY

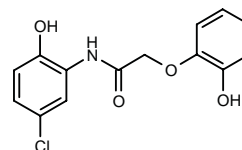
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SOURCE – Emisphere Technologies.

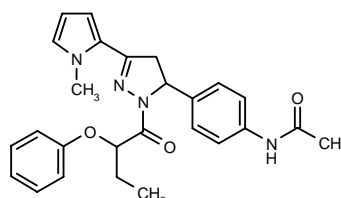
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PHARMACOLOGICAL TOOLS

318270

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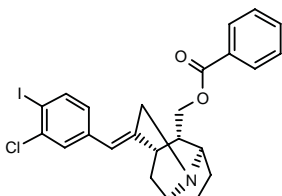


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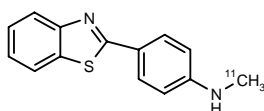
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SOURCE – University of Pittsburgh, Pittsburgh, PA (US).

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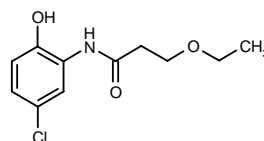
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DRUG DELIVERY

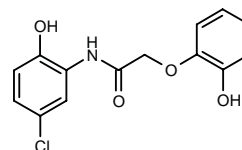
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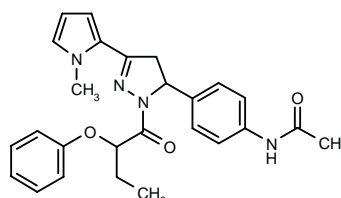
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PHARMACOLOGICAL TOOLS

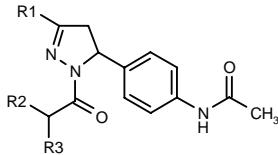
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C₂₆ H₂₈ N₄ O₃; Mol wt: 444.5322

ACTION – Kappa opioid receptor ligand (IC_{50} = 17.5 nM) with high selectivity over mu and delta opioid receptors (IC_{50} = 430 and > 10,000 nM, respectively). Compound showed a good pharmacokinetic profile in rats with low clearance (8 ml/min/kg) and high oral bioavailability (42%). Other related compounds are:



Compound	R1	R2	R3	Formula
318271	1-Me-2-pyrrolyl	H	4-Cl-Ph	C ₂₄ H ₂₃ ClN ₄ O ₂
318272	2-Pyr	Et	OPh	C ₂₆ H ₂₆ N ₄ O ₃

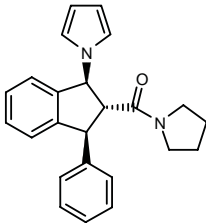
SOURCE – AstraZeneca.

REFERENCES

1. Semple, G. et al. *N-Substituted 2-pyrazolines are opioid receptor ligands*. 223rd ACS Natl Meet (April 7-11, Orlando) 2002, Abst MEDI 43.

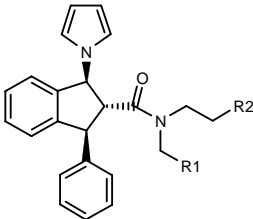
318543

trans,trans-1-[1-Phenyl-3-(1*H*-pyrrol-1-yl)-2,3-dihydro-1*H*-inden-2-yl]-1-(pyrrolidin-1-yl)methanone



C₂₄ H₂₄ N₂ O; Mol wt: 356.4666

ACTION – Nonpeptide tachykinin NK₂ receptor ligand (IC_{50} = 1.9 μ M, K_i = 0.633 μ M) with high selectivity over NK₁ and NK₃ receptors (IC_{50} > 10 μ M). Other related compounds are:



Compound	R1	R2	Formula
318542	Me	H	C ₂₄ H ₂₆ N ₂ O
318544	H	Ph	C ₂₉ H ₂₈ N ₂ O

SOURCE – Sanofi-Synthélabo.

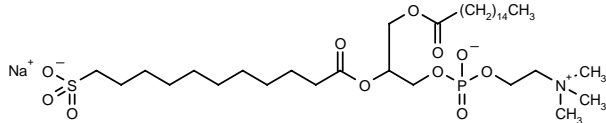
REFERENCES

1. Guillon, J. et al. *Synthesis of a novel class of non-peptide NK-2 receptor ligand, derived from 1-phenyl-3-pyrrol-1-ylidan-2-carboxamides*. Bioorg Med Chem 2002, 10(4): 1043.

PHARMACEUTICAL AIDS

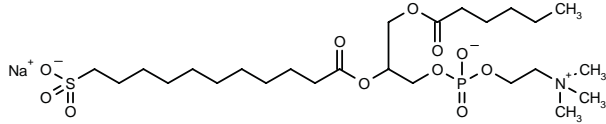
316995

1-Hexadecanoyl-2-(11-sulfoundecanoyl)-*sn*-glycero-3-phosphatidylcholine sodium salt



C₃₅ H₆₉ N Na O₁₁ P S; Mol wt: 765.9561

ACTION – Agent with the ability to inhibit the metabolism of active peptides such as brain-derived neurotrophic factor (BDNF), erythropoietin, thrombopoietin, urokinase-type plasminogen activator (uPA), etc. It is reported to form noncovalent complexes with active peptides, thus preventing their metabolism, resulting in lower therapeutic doses of such peptides and fewer side effects. Compound was shown to potentiate the glucose-lowering effect of BDNF (5 mg/kg) when administered to mice at a dose of 28.4 mg/kg i.v. Another exemplified sulfonic acid derivative is:



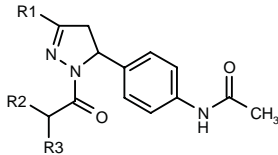
316996: C₂₅ H₄₉ N Na O₁₁ P S

SOURCE – Sumitomo Pharmaceuticals.

REFERENCES

1. Itakura, Y. and Ueki, Y. (Sumitomo Pharmaceuticals Co., Ltd.) *Sulfonic acid derivs*. JP 2002020393.

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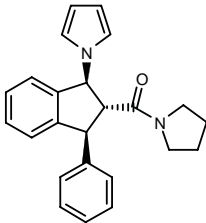
SOURCE – AstraZeneca.

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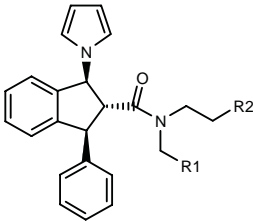
318543

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318544	H	Ph	C ₂₉ H ₂₈ N ₂ O

SOURCE – Sanofi-Synthélabo.

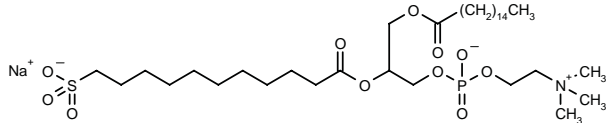
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PHARMACEUTICAL AIDS

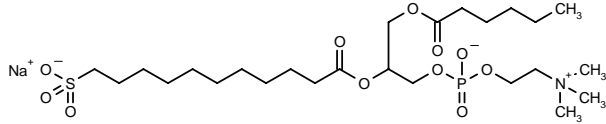
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C₃₅ H₆₉ N Na O₁₁ P S; Mol wt: 765.9561

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SOURCE – Sumitomo Pharmaceuticals.

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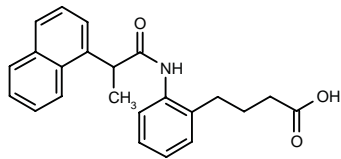
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ANALGESIC AND ANESTHETIC
DRUGS

ANALGESIC DRUGS

318441

4-[2-[2-(1-Naphthyl)propionamido]phenyl]butyric acid



C23 H23 N O3; Mol wt: 361.4387

ACTION – A representative compound from a series of carboxamide compounds effective as antagonists at PGE₂ receptors, particularly the EP₃ and/or EP₄ receptor subtype. This compound displayed K_i values of 2.4 and 0.3 μM, respectively, at EP₃ and EP₄ receptors in binding assays, and selectivity over EP₁ and EP₂ receptor subtypes. Potentially useful for the treatment of pain, allergy, Alzheimer's disease and cancer.

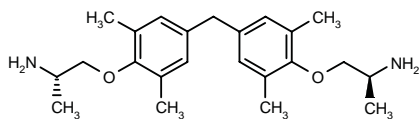
SOURCE – Ono.

REFERENCES

1. Tani, K. et al. (Ono Pharmaceutical Co., Ltd.) *Carboxylic acid derivs., process for producing the same and drugs containing the same as the active ingredient*. WO 0216311.

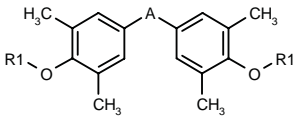
318463

2,2'-Methylenebis(2,6-dimethyl-4,1-phenylene)bis-(oxy)bis[1(S)-methylethylamine]

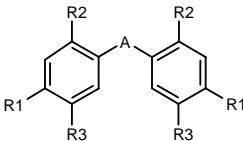


C23 H34 N2 O2; Mol wt: 370.5336

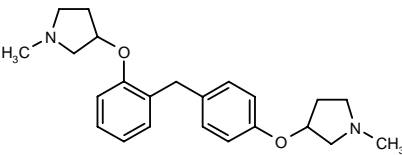
ACTION – Sodium channel blocker, as demonstrated *in vitro* in rat cerebellar granule neurons. Potentially useful for the treatment of neuropathic pain. Other exemplified compounds are:



Compound	R1	A	Formula
318464	1-Me-2-Pip-CH2CH2	-CH2-	C ₃₃ H ₅₀ N ₂ O ₂
318466	2(R)-Me-4(S)-pyrrolidinyl	-CH2-	C ₂₇ H ₃₈ N ₂ O ₂
318467	1-Me-3-pyrrolidinyl	-C(Me)2-	C ₂₉ H ₄₂ N ₂ O ₂
318468	1-Me-3-pyrrolidinyl	-(CH2)2-	C ₂₈ H ₄₀ N ₂ O ₂



Compound	R1	R2	R3	A	Formula
318470	H	OCH2C(Me)2-CH2N(Me)2	Cl	CH2	C ₂₇ H ₄₀ Cl ₂ N ₂ O ₂
318471	4-morpholinyl-CH2CH2O	H	Cl	CH2	C ₂₅ H ₃₂ Cl ₂ N ₂ O ₄
318473	1-Me-3-Pip-CH2O	H	H	O	C ₂₆ H ₃₆ N ₂ O ₃



318469: C23 H30 N2 O2

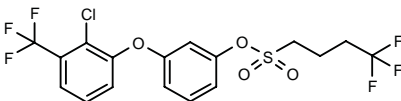
SOURCE – Advanced Medicine.

REFERENCES

1. Chinn, J.P. et al. (Advanced Medicine, Inc.) *Sodium channel modulators*. WO 0218334.

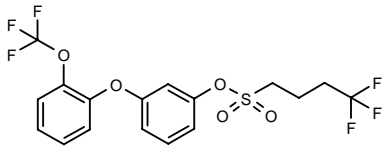
318658

4,4,4-Trifluorobutane-1-sulfonic acid 3-[2-chloro-3-(trifluoromethyl)phenoxy]phenyl ester



C17 H13 Cl F6 O4 S; Mol wt: 462.7927

ACTION – Cannabinoid receptor agonist with potential in the treatment of pain and neurodegenerative diseases, particularly Parkinson’s disease. The compound was shown to induce a decrease in body temperature following oral administration to rats (1 °C at a dose of 10 mg/kg), suggesting agonist activity at cannabinoid CB₁ receptors. Another exemplified phenoxyphenyl-containing sulfonic acid derivative is:



318659: C17 H14 F6 O5 S

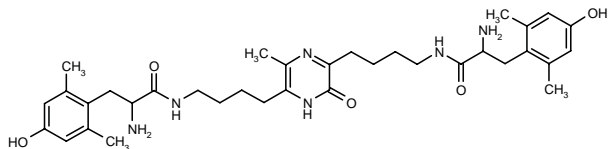
SOURCE – Bayer.

REFERENCES

1. Heil, M. et al. (Bayer AG) *Phenoxyphenyl alkane sulfonates*. WO 0226702.

318958

*N*¹,*N*^{1'}-(3-Methyl-6-oxo-1,6-dihydropyrazin-2,5-diyl)-bis(1,4-butylene)bis(4-hydroxy-2,6-dimethyl-DL-phenyl-alaninamide)



C35 H50 N6 O5; Mol wt: 634.8170

ACTION – Potential analgesic agent, a representative compound from a series of opioid peptide derivatives with affinity for mu opioid receptors. Compound bound to mu opioid receptors in rat brain preparations with a K_i of 0.114 nM, and exhibited 200-fold selectivity over delta opioid receptors. In functional assays, it was able to inhibit electrical stimulation-induced contractions in guinea pig ileum (mediated by mu opioid receptors) and mouse vas deferens (mediated by delta opioid receptors) with IC₅₀ values of 1.90 and 41.5 nM, respectively, suggesting agonist activity. In the mouse writhing test, compound demonstrated analgesic activity at a dose of 0.06 µg i.v.

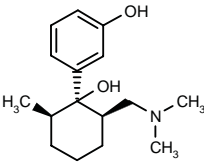
SOURCE – Teikoku Seiyaku.

REFERENCES

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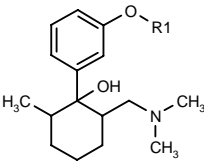
319131

3-[(1*R**,2*R**,6*R**)-2-(Dimethylaminomethyl)-1-hydroxy-6-methylcyclohexyl]phenol



C16 H25 N O2; Mol wt: 263.3785

ACTION – Analgesic agent useful for the treatment of acute and chronic pain including neuropathic pain, migraine, hyperalgesia and allodynia. The compound gave ED₅₀ values of 2.09 mg/kg p.o. and 2.15 mg/kg i.v., respectively, when tested *in vivo* in the mouse writhing and tail-flick tests. Other exemplified tramadol derivatives are:



Compound	R1	Isomer	Formula
319132	allyl	1 <i>R</i> *,2 <i>R</i> *,6 <i>R</i> *	C ₁₉ H ₂₉ NO ₂
319133	Me	1 <i>S</i> ,2 <i>S</i> ,6 <i>S</i>	C ₁₇ H ₂₇ NO ₂
319134	Me	1 <i>R</i> ,2 <i>R</i> ,6 <i>R</i>	C ₁₇ H ₂₇ NO ₂
319135	H	1 <i>S</i> ,2 <i>S</i> ,6 <i>S</i>	C ₁₆ H ₂₅ NO ₂
319136	H	1 <i>R</i> ,2 <i>R</i> ,6 <i>R</i>	C ₁₆ H ₂₅ NO ₂
319137	Et	1 <i>R</i> ,2 <i>R</i> ,6 <i>R</i>	C ₁₈ H ₂₉ NO ₂
319138	cyclopentyl	1 <i>R</i> ,2 <i>R</i> ,6 <i>R</i>	C ₂₁ H ₃₃ NO ₂
319139	cyclobutyl-CH ₂	1 <i>R</i> ,2 <i>R</i> ,6 <i>R</i>	C ₂₁ H ₃₃ NO ₂

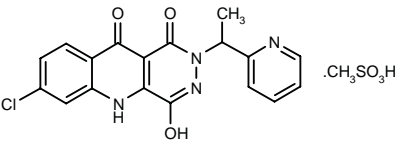
SOURCE – Grünenthal.

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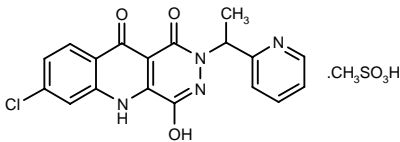
319221

(–)-7-Chloro-4-hydroxy-2-[1-(2-pyridyl)ethyl]-1,2,5,10-tetrahydropyridazino[4,5-*b*]quinoline-1,10-dione methane-sulfonate



C18 H13 Cl N4 O3 . C H4 O3 S; Mol wt: 464.8843

ACTION – Agent with affinity for the glycine site of NMDA receptors shown to inhibit the binding of [³H]-MDL-105519 to NMDA receptors in rat brain preparations with a K_i value of 194 nM. Potentially useful as an analgesic agent, as demonstrated in a rat model of neuropathic pain, with an oral minimum effective dose (MED) of 5 mg/kg/day. Other exemplified 4-hydroxypyridazino[4,5-*b*]quinoline-1,10-dione derivatives are:



Compound	Isomer	Formula
319222	(+)	C ₁₈ H ₁₃ ClN ₄ O ₃ ·CH ₄ O ₃ S
319223	racemic	C ₁₈ H ₁₃ ClN ₄ O ₃ ·CH ₄ O ₃ S

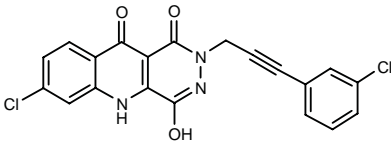
SOURCE – AstraZeneca.

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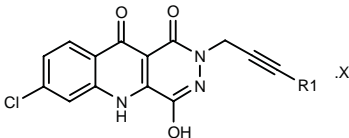
319227

7-Chloro-2-[3-(3-chlorophenyl)-2-propynyl]-4-hydroxy-1,2,5,10-tetrahydropyridazino[4,5-b]quinoline-1,10-dione



C20 H11 Cl2 N3 O3; Mol wt: 412.2309

ACTION – Agent with affinity for the glycine site of NMDA receptors shown to inhibit the binding of [³H]-MDL-105519 to NMDA receptors in rat brain preparations with a K_i value of 7.86 nM. Potentially useful as an analgesic agent. Other exemplified 4-hydroxypyridazino[4,5-*b*]quinoline-1,10-dione derivatives are:



Compound	R1	X	Formula
319228	4-Pyr	3MeSO3H	C ₁₉ H ₁₁ ClN ₄ O ₃ ·3CH ₄ O ₃ S
319229	4-Cl-Ph		C ₂₀ H ₁₁ Cl ₂ N ₃ O ₃
319230	2-Cl-Ph		C ₂₀ H ₁₁ Cl ₂ N ₃ O ₃
319231	3-Pyr	MeSO3H	C ₁₉ H ₁₁ ClN ₄ O ₃ ·CH ₄ O ₃ S
319232	6-Cl-3-Pyr		C ₁₉ H ₁₁ ClN ₄ O ₃

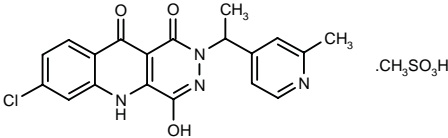
SOURCE – AstraZeneca.

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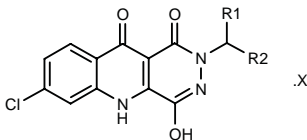
319235

(±)-7-Chloro-4-hydroxy-2-[1-(2-methylpyridin-4-yl)ethyl]-1,2,5,10-tetrahydropyridazino[4,5-*b*]quinoline-1,10-dione methanesulfonate



C19 H15 Cl N4 O3 . C H4 O3 S; Mol wt: 478.9111

ACTION – Agent with affinity for the glycine site of NMDA receptors that was shown to inhibit the binding of [³H]-MDL-105519 to NMDA receptors in rat brain preparations with a K_i of 228 nM. Potentially useful as an analgesic agent. Other exemplified 4-hydroxypyridazino[4,5-*b*]quinoline-1,10-dione derivatives are:



Compound	R1	R2	X	Formula
319236	2-Pyr	cyclopropyl		C ₂₀ H ₁₅ ClN ₄ O ₃
319237	4-Pyr	cyclopropyl	HCl	C ₂₀ H ₁₅ ClN ₄ O ₃ ·HCl
319239	4-Pyr	Ph		C ₂₃ H ₁₅ ClN ₄ O ₃
319240	3-Me-4-Pyr	Me		C ₁₉ H ₁₅ ClN ₄ O ₃
319241	3-Me-2-Pyr	Me	MeSO3H	C ₁₉ H ₁₅ ClN ₄ O ₃ ·CH ₄ O ₃ S
319242	1-oxido-2-Pyr	Me		C ₁₉ H ₁₅ ClN ₄ O ₄
319243	1-oxido-4-Pyr	Me		C ₁₈ H ₁₃ ClN ₄ O ₄

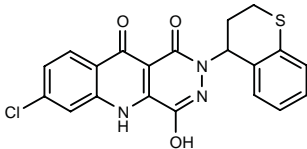
SOURCE – AstraZeneca.

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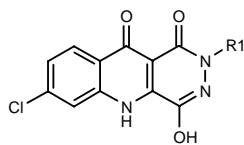
319246

(±)-7-Chloro-2-(3,4-dihydro-2*H*-1-benzothiopyran-4-yl)-4-hydroxy-1,2,5,10-tetrahydropyridazino[4,5-*b*]quinoline-1,10-dione



C20 H14 Cl N3 O3 S; Mol wt: 411.8676

ACTION – Agent with affinity for the glycine site of NMDA receptors shown to inhibit the binding of [³H]-MDL-105519 to NMDA receptors in rat brain preparations with a K_i value of 411 nM. Potentially useful as an analgesic agent, as demonstrated in a rat model of neuropathic pain, with an oral minimum effective dose (MED) of 30 mg/kg/day. Other exemplified 4-hydroxypyridazino[4,5-*b*]quinoline-1,10-dione derivatives are:



Compound	R1	Formula
319249	3,4-dyhydro-2H-benzopyran-4-yl	C ₂₀ H ₁₄ ClN ₃ O ₄
319251	4,5,6,7-tetrahydro-4-benzothienyl	C ₁₉ H ₁₄ ClN ₃ O ₃ S
319252	1,2,3,4-tetrahydro-1-Naph	C ₂₁ H ₁₆ ClN ₃ O ₃

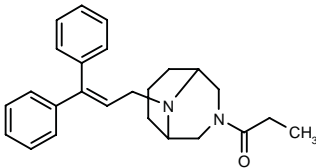
SOURCE – AstraZeneca.

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319345

9-(3,3-Diphenyl-2-propenyl)-3-propionyl-3,9-diazabicyclo[3.3.1]nonane



C25 H30 N2 O; Mol wt: 374.5250

ACTION – Potent and selective mu opioid receptor agonist with high affinity and selectivity for mu receptors over delta and kappa opioid receptors (K_i = 5, 630 and 2430 nM, respectively). It showed strong analgesic activity in the mouse hot-plate test (ED₅₀ = 3.88 mg/kg i.p.), comparing favorably to morphine (ED₅₀ = 5 mg/kg i.p.); its activity was completely reversed by pretreatment with the opioid antagonist naloxone. Tolerance developed in mice only after double the treatment period for morphine.

SOURCES – Università degli Studi di Cagliari, Cagliari (IT); Centro Consortile Ricerche Neuropsicofarmacologiche, Cagliari (IT); Università degli Studi di Milano, Milano (IT); Università degli Studi di Sassari, Sassari (IT).

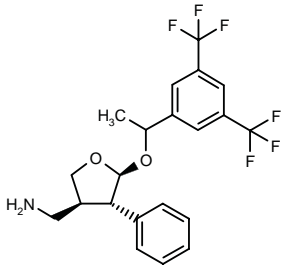
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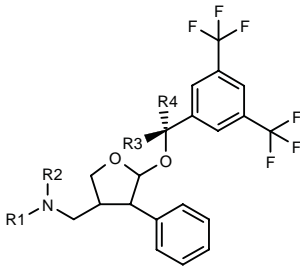
319495

(3*R**,4*R**,5*R**)-5-[1-[3,5-Bis(trifluoromethyl)phenyl]ethoxy]-4-phenyltetrahydrofuran-3-ylmethylamine

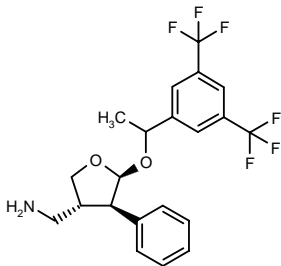


C21 H21 F6 N O2; Mol wt: 433.3899

ACTION – Tachykinin NK₁ receptor antagonist, potentially useful for the treatment of pain, inflammation, migraine, emesis, postherpetic neuralgia, depression and anxiety. Other exemplified tetrahydrofuran derivatives are:



Compound	R1	R2	R3	R4	Isomer	Formula
319496	Me	Me	Me	H	3 <i>R</i> *,4 <i>R</i> *,5 <i>R</i> *	C ₂₃ H ₂₅ F ₆ NO ₂
319497	H	H	CH2OH	H	2 <i>S</i> *,3 <i>S</i> *,4 <i>S</i> *	C ₂₁ H ₂₁ F ₆ NO ₃
319498	H	H	CH2OH	H	2 <i>R</i> *,3 <i>R</i> *,4 <i>R</i> *	C ₂₁ H ₂₁ F ₆ NO ₃
319499	Me	Me	CH2OH	H	2 <i>S</i> *,3 <i>S</i> *,4 <i>S</i> *	C ₂₃ H ₂₅ F ₆ NO ₃
319501	Me	Me	H	Me	3 <i>R</i> *,4 <i>R</i> *,5 <i>S</i> *	C ₂₃ H ₂₅ F ₆ NO ₂
319502	H	H	CH2OH	H	2 <i>R</i> *,3 <i>S</i> *,4 <i>S</i> *	C ₂₁ H ₂₁ F ₆ NO ₃
319503	H	H	H	CH2OH	2 <i>R</i> *3 <i>S</i> *,4 <i>S</i> *	C ₂₁ H ₂₁ F ₆ NO ₃



319500: C21 H21 F6 N O2

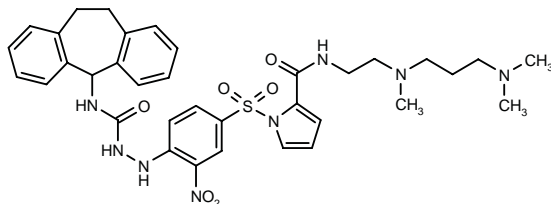
SOURCE – Merck Sharp & Dohme.

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319819

4-(10,11-Dihydro-5*H*-dibenzo[*a,d*]cyclohepten-5-yl)-1-[4-[2-[*N*-[2-[*N*-[3-(dimethylamino)propyl]-*N*-methylamino]ethyl]carbamoyl]-1*H*-pyrrol-1-ylsulfonyl]-2-nitrophenyl]-semicarbazide



C35 H42 N8 O6 S; Mol wt: 702.8328

ACTION – Potent, orally active bradykinin B₂ receptor antagonist with nanomolar affinity for human B₂ receptors expressed in COS-7 cells (K_i = 2.79 nM) and > 1,000-fold selectivity over a number of other receptors including B₁, M₁ and NK₁ receptors. Compound inhibited B₂ receptor-mediated Ca²⁺ efflux from NG105-15 cells (IC₅₀ = 141 nM) and contractions of rat uterus smooth muscle (IC₅₀ = 1.9 nM); in rats, it produced a long-lasting (4 h) reversal of mechanical hyperalgesia induced by Freund's complete adjuvant or turpentine (ED₅₀ = 0.02 and 0.22 mg/kg p.o., respectively). Potentially useful for the treatment of painful inflammatory conditions.

SOURCE – Novartis.

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ETORICOXIB⁺

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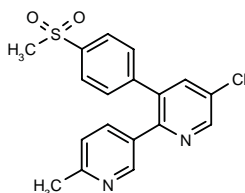
5-Chloro-3-[4-(methylsulfonyl)phenyl]-2-(6-methylpyridin-3-yl)pyridine

5-Chloro-6'-methyl-3-[4-(methylsulfonyl)phenyl]-2,3'-bipyridine

L-791456

MK-0663

MK-663



C18 H15 Cl N2 O2 S; Mol wt: 358.8475

ACTION – Nonsteroidal antiinflammatory drug (NSAID), an orally active and highly selective cyclooxygenase type 2 (COX-2) inhibitor.

INDICATION – Symptomatic relief of osteoarthritis, rheumatoid arthritis, acute gouty arthritis, chronic musculoskeletal pain, dental surgery pain and primary dysmenorrhea.

PRESENTATION – Film-coated tablets, 60, 90 and 120 mg.

PROPRIETARY NAME – Arcoxia (GB).

SOURCE – Merck & Co.

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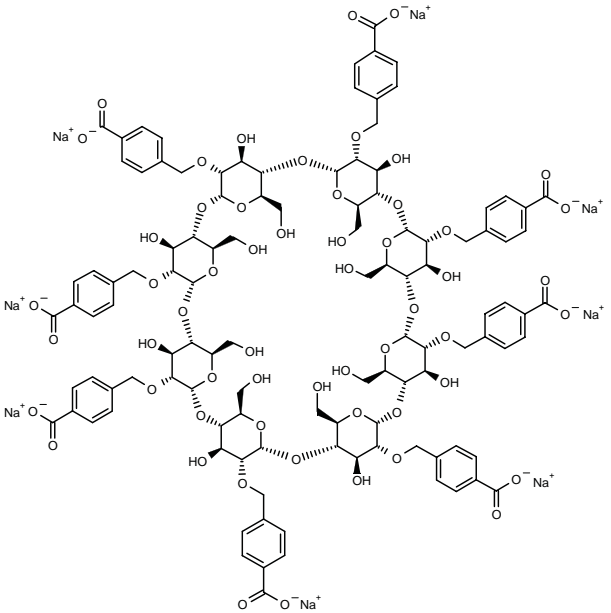
*Drug Data Rep 2000, 022(10): 0926.

ADJUNCTS TO ANESTHESIA

ORG-25819

319300

2-O-Octa(4-carboxybenzyl)-γ-cyclodextrin octasodium salt



C112 H120 Na8 O56; Mol wt: 2546.0440

ACTION – Reversal agent for neuromuscular blockers (NMBs), a 2-O-substituted cyclodextrin whose activity results from chemical encapsulation of the NMB inside the cyclodextrin cavity. The biological activity of compound was examined *in vitro* ($EC_{50} = 7.2 \mu M$ in isolated mouse hemidiaphragm) and in anesthetized guinea pigs, where it strongly reversed the neuromuscular block induced by rocuronium bromide ($ED_{50} = 0.21 \mu mol/kg$ i.v.) without inducing significant changes in heart rate or mean arterial blood pressure.

SOURCE – Organon.

REFERENCES

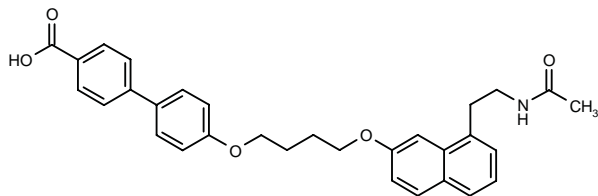
1. Tarver, G.J. et al. *2-O-Substituted cyclodextrins as reversal agents for the neuromuscular blocker rocuronium bromide*. Bioorg Med Chem 2002, 10(6): 1819.

PSYCHOPHARMACOLOGIC DRUGS

TREATMENT OF SLEEP DISORDERS

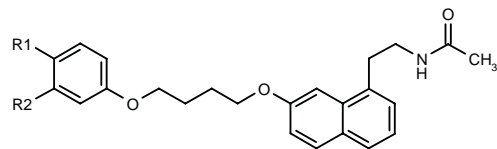
319281

4'-[4-[8-(2-Acetamidoethyl)naphthalen-2-yloxy]butoxy]-biphenyl-4-carboxylic acid



C31 H31 N O5; Mol wt: 497.5879

ACTION – Agent with affinity for melatonin receptors, potentially useful for the treatment of disorders associated with the melatonergic system, particularly seasonal depression, sleep disorders, cardiovascular disorders, eating disorders and obesity. Other exemplified biphenyl derivatives include the following:



Compound	R1	R2	Formula
319282	4-(CO2Me)-Ph	H	C ₃₂ H ₃₃ NO ₅
319283	4-(CH2OH)-Ph	H	C ₃₁ H ₃₃ NO ₄
319284	Ph	H	C ₃₀ H ₃₁ NO ₃
319285	H	Ph	C ₃₀ H ₃₁ NO ₃

SOURCE – Servier.

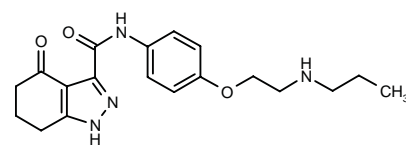
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ANXIOLYTICS

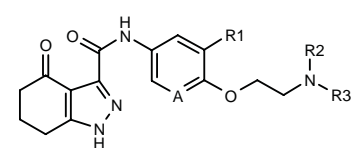
319093

4-Oxo-*N*-[4-[2-(propylamino)ethoxy]phenyl]-4,5,6,7-tetrahydro-1*H*-indazole-3-carboxamide



C19 H24 N4 O3; Mol wt: 356.4236

ACTION – A selective ligand of the benzodiazepine site of GABA_A receptors, expected to be useful for the treatment of anxiety, depression, sleep disorders and cognitive impairment. Other exemplified tetrahydroindazoles are:



Compound	R1	R2	R3	A	Formula
319094	F	-CH2CH2OCH2CH2-		CH	C ₂₀ H ₂₃ FN ₄ O ₄
319095	H	Pr	H	N	C ₁₈ H ₂₃ N ₅ O ₃
319096	H	Et	H	N	C ₁₇ H ₂₁ N ₅ O ₃

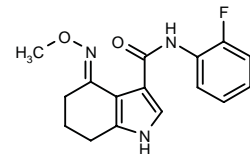
SOURCE – Neurogen.

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1. Maynard, G. et al. (Neurogen Corp.) *Aryl substd. tetrahydroindazoles and their use as ligands for the GABA_A receptor*. WO 0220492.

319097

N-(2-Fluorophenyl)-4-(methoxyimino)-4,5,6,7-tetrahydro-1*H*-indole-3-carboxamide



C16 H16 F N3 O2; Mol wt: 301.3194

ACTION – A selective ligand of the benzodiazepine site of GABA_A receptors, expected to be useful for the treatment of anxiety, depression, sleep disorders and cognitive impairment.

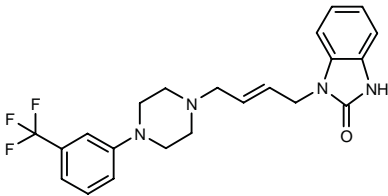
SOURCE – Neurogen.

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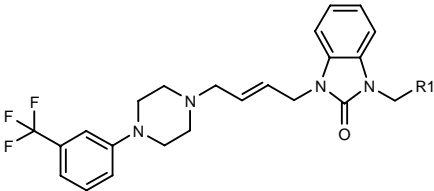
319447

1-[4-[4-[3-(Trifluoromethyl)phenyl]piperazin-1-yl]-2(*E*)-butenyl]-2,3-dihydro-1*H*-benzimidazol-2-one



C22 H23 F3 N4 O; Mol wt: 416.4447

ACTION – Agent with affinity for the 5-HT_{1A} receptor (IC₅₀ = 4.8 nM) also proven to inhibit forskolin-stimulated cAMP production in 5-HT_{1A}-transfected CHO cells, suggesting agonist activity. Potentially useful for the treatment of anxiety, depression, psychosis, schizophrenia, eating disorders, sexual disorders, Parkinson’s disease, stroke and traumatic brain injury. Other exemplified 2,3-dihydro-1*H*-benzimidazol-2-one derivatives are:



Compound	R1	Isomer	Formula
319449	H	Z	C ₂₃ H ₂₅ F ₃ N ₄ O
319451	Et	Z	C ₂₅ H ₂₉ F ₃ N ₄ O
319452	H	E	C ₂₃ H ₂₅ F ₃ N ₄ O

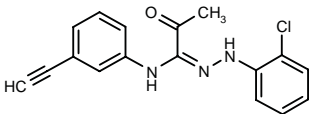
SOURCE – Boehringer Ingelheim.

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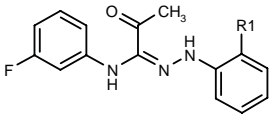
319838

N'-(2-Chlorophenyl)-*N*-(3-ethynylphenyl)-2-oxopropane-hydrazoneamide



C17 H14 Cl N3 O; Mol wt: 311.7706

ACTION – Corticotropin-releasing factor CRF₁ receptor antagonist (K_i = 35 nM) potentially useful for the treatment of anxiety and depression. Other related arylamidrazones are:



Compound	R1	Formula
319839	Me	C ₁₆ H ₁₆ FN ₃ O
319840	Cl	C ₁₅ H ₁₃ ClFN ₃ O

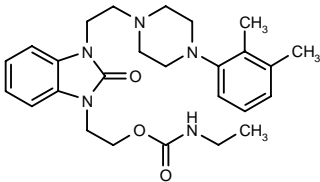
SOURCE – Bristol-Myers Squibb.

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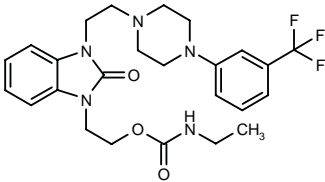
320057

N-Ethylcarbamic acid 2-[3-[2-[4-(2,3-dimethylphenyl)-piperazin-1-yl]ethyl]-2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl]ethyl ester



C26 H35 N5 O3; Mol wt: 465.5945

ACTION – Agent with affinity for 5-HT and dopamine receptors that was shown to be active at 5-HT_{1A} (IC₅₀ = 0.85 nM), 5-HT_{2A} (IC₅₀ = 3.2 nM) and D4 receptors (48% inhibition of [³H]-YM-09151-2 binding at 0.1 μM) in binding assays. In functional assays, this compound demonstrated 5-HT_{1A}-agonist and 5-HT_{2A}-antagonist activity. It is considered to have potential in the treatment of anxiety and affective disorders, as well as depression, psychosis, schizophrenia, eating disorders, sexual disorders, Parkinson’s disease, stroke and traumatic brain injury. Another exemplified benzimidazoline derivative is:



320058: C25 H30 F3 N5 O3

SOURCE – Boehringer Ingelheim.

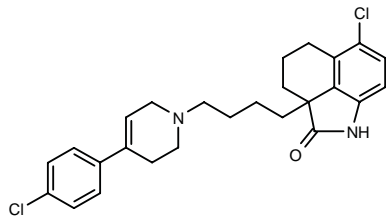
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ANTIPSYCHOTIC DRUGS

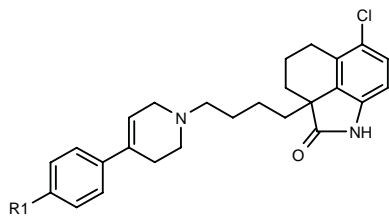
318748

6-Chloro-2a-[4-[4-(4-chlorophenyl)-1,2,3,6-tetrahydropyridin-1-yl]butyl]-1,2,2a,3,4,5-hexahydrobenzo[cd]indol-2-one



C26 H28 Cl2 N2 O; Mol wt: 455.4262

ACTION – Agent with affinity for 5-HT₇ receptors (K_i = 7 nM) and > 140-fold selectivity over 5-HT₂ receptors. Using human liver preparations, compound demonstrated superior metabolic stability compared to a reference compound. Potentially useful for the treatment of manic–depressive psychosis, anxiety, schizophrenia, epilepsy, sleep disorders, biorhythm disorders, migraine, circulatory disorders such as hypertension and digestive function failure. Other exemplified tetrahydrobenzindole derivatives are:



Compound	R1	Formula
318749	F	C ₂₆ H ₂₈ ClFN ₂ O
318750	Br	C ₂₆ H ₂₈ BrClN ₂ O

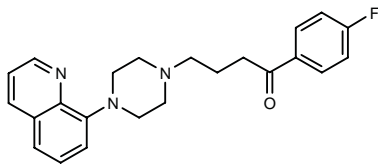
SOURCE – Meiji Seika.

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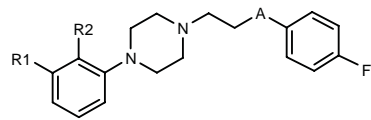
319037

1-(4-Fluorophenyl)-4-[4-(8-quinoliny)piperazin-1-yl]butan-1-one



C23 H24 F N3 O; Mol wt: 377.4606

ACTION – Antipsychotic agent that acts as an agonist at 5-HT_{1A} and/or dopamine D2 receptors, expected to be useful for the treatment of schizophrenia. Other specifically claimed 1-arylpiperazine derivatives are:



Compound	R1,R2	A	Formula
319038	-NHCH=CH-	-CH2CH(OH)-	C ₂₂ H ₂₆ FN ₃ O
319039	-NHCH=CH-	-CH2CO-	C ₂₂ H ₂₄ FN ₃ O
319040	-CH=CHCH=N-	-C(OH)(4-F-Ph)-	C ₂₈ H ₂₇ F ₂ N ₃ O
319041	-CH=CHCH=N-	-CH2CH(OH)-	C ₂₃ H ₂₈ FN ₃ O
319042	-CH=CHC(Me)=N-	-CH2CH(OH)-	C ₂₄ H ₂₈ FN ₃ O
319043	-CH=CHC(Me)=N-	-CH2CO-	C ₂₄ H ₂₆ FN ₃ O
319044	-CH=CHC(Me)=N-	-CH2(OH)(4-F-Ph)-	C ₃₀ H ₃₁ F ₂ N ₃ O

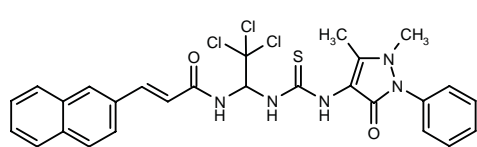
SOURCE – Merck KGaA.

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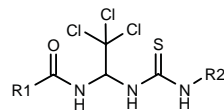
319311

3-(2-Naphthyl)-N-[2,2,2-trichloro-1-[3-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)thioureido]ethyl]-2(E)-propenamide



C27 H24 Cl3 N5 O2 S; Mol wt: 588.9446

ACTION – An inhibitor of glycine GlyT-1 transporter activity, as demonstrated by inhibition of high-affinity glycine uptake in astrocytoma cells. Potentially useful for the treatment of neurological disorders such as schizophrenia, dementia, epilepsy, muscle spasticity, mood disorders, learning disorders, neurodegenerative diseases and pain. Other exemplified nitrogen-containing compounds are:



Compound	R1	R2	Formula
319312	CH=CHPh	8-quinolyl	C ₂₁ H ₁₇ Cl ₃ N ₄ OS
319313	2-Naph	8-quinolyl	C ₂₃ H ₁₇ Cl ₃ N ₄ OS
319314	CH=CHPh	2-cyclopropyl-2,3-dihydro-1H-tetrazol-5-yl	C ₁₆ H ₁₈ Cl ₃ N ₇ OS
319315	cyclohexyl	2-CO2H-Ph	C ₁₇ H ₂₀ Cl ₃ N ₃ O ₃ S
319316	t-Bu	2-NO2-Ph	C ₁₄ H ₁₇ Cl ₃ N ₄ O ₃ S
319317	t-Bu	2-Ac-Ph	C ₁₆ H ₂₀ Cl ₃ N ₃ O ₂ S
319318	cyclohexyl	CH2CO2Me	C ₁₃ H ₂₀ Cl ₃ N ₃ O ₃ S
319319	cyclohexyl	4-F-2-CO2H-Ph	C ₁₇ H ₁₉ Cl ₃ FN ₃ O ₃ S

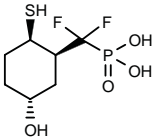
SOURCE – Gliatech.

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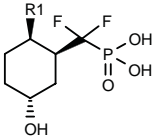
319413

1,1-Difluoro-1-[(1*R*,2*R*,5*R*)-5-hydroxy-2-sulfanylcyclohexyl]-1-methylphosphonic acid



C7 H13 F2 O4 P S; Mol wt: 262.2117

ACTION – Inositol monophosphatase (IMPase) inhibitor, giving a K_i of 0.9 μ M against bovine brain-derived IMPase. Potentially useful for the treatment of mania and manic-depressive psychosis. Other exemplified difluoromethylphosphonic acid derivatives are:



Compound	R1	Formula
319414	OH	C ₇ H ₁₃ F ₂ O ₅ P
319415	NH2	C ₇ H ₁₄ F ₂ NO ₄ P

SOURCE – Hisamitsu.

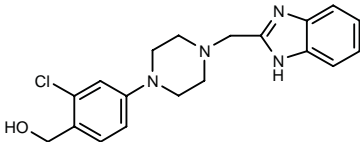
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PD-89211

318641

1-[4-[4-(1*H*-Benzimidazol-2-ylmethyl)piperazin-1-yl]-2-chlorophenyl]methanol



C19 H21 Cl N4 O; Mol wt: 356.8549

ACTION – High-affinity dopamine D4.2 ligand (K_i = 3.6 nM) with high selectivity over other dopamine receptor subtypes, adrenoceptors and 5-HT receptors (K_i > 3000 nM) and other neurotransmitters. Compound exhibited functional antagonism in CHO cells expressing human D4.2 receptors (IC_{50} = 2.1 nM for reversal of quinpirole-induced mitogenesis) but had no effect on dopamine turnover, indicating a low propensity for producing motor side effects. In addition, it increased DOPA synthesis in

the hippocampus of wild-type mice but not in mice lacking D4 receptors. Potentially useful for the treatment of schizophrenia and as a pharmacological tool.

SOURCE – Pfizer.

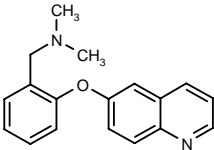
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TREATMENT OF MOOD DISORDERS

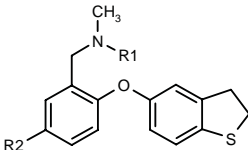
318356

N,N-Dimethyl-*N*-[2-(quinolin-6-yloxy)benzyl]amine



C18 H18 N2 O; Mol wt: 278.3532

ACTION – Selective inhibitor of 5-HT reuptake by 5-HT transporters (SERT), as demonstrated in human SERT-transfected HEK293 cells (IC_{50} = 2.0 nM). Potentially useful for the treatment of depression, attention deficit hyperactivity disorder, obsessive-compulsive disorder, posttraumatic stress disorder, substance abuse disorders and sexual dysfunctions, particularly premature ejaculation. Other exemplified 2-phenoxybenzylamine derivatives are:



Compound	R1	R2	Formula
318358	Me	SO2NH2	C ₁₇ H ₂₀ N ₂ O ₃ S ₂
318359	H	CONHMe	C ₁₈ H ₂₀ N ₂ O ₂ S

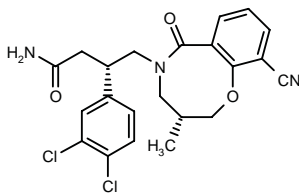
SOURCE – Pfizer.

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318874

4-[10-Cyano-3(*R*)-methyl-6-oxo-3,4,5,6-tetrahydro-2*H*-1,5-benzoxazocin-5-yl]-3(*S*)-(3,4-dichlorophenyl)butyramide



C22 H21 Cl2 N3 O3; Mol wt: 446.3319

ACTION – A representative compound from a series of cyclized benzamide derivatives with tachykinin NK₁ receptor-antagonist activity. Potentially useful for the treatment of depression, anxiety, eating disorders, stress disorders, bipolar disorder, drug abuse, schizophrenia, psychoses, movement disorders, cognitive disorders, aggressive behavior, obesity, emesis, rheumatoid arthritis, Alzheimer's disease, cancer, edema, allergic rhinitis, migraine, bladder hypermotility and urticaria.

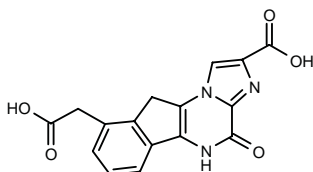
SOURCE – AstraZeneca.

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NEUROLOGIC DRUGS**ANTIEPILEPTIC DRUGS****RPR-117824****295128**

9-(Carboxymethyl)-4-oxo-5,10-dihydro-4*H*-imidazo[1,2-*a*]-indeno[1,2-*e*]pyrazine-2-carboxylic acid



C16 H11 N3 O5; Mol wt: 325.2789

ACTION – Potent AMPA antagonist with high affinity for AMPA receptors and selectivity over NMDA receptors (IC₅₀ = 18 and 7200 nM, respectively). In functional studies, compound competitively inhibited the electrophysiological responses mediated by AMPA receptors expressed in *Xenopus* oocytes and in rat brain (IC₅₀ = 0.36 μM). It displayed anticonvulsant activity in several *in vivo* models including supramaximal electroshock seizures in mice (ED₅₀ = 0.83 mg/kg i.p.) and generalized

clonic seizures induced by chemoconvulsants including pentylenetetrazol, bicuculline and isoniazid (ED₅₀ = 1.5-1.7 mg/kg s.c.). In addition, it exhibited neuroprotective activity in a global ischemia model in gerbils and a focal ischemia model in rats, as well as in traumatic brain injury and spinal cord injury models in rats. Potentially useful for the treatment of epilepsy and stroke.

SOURCE – Aventis Pharma.

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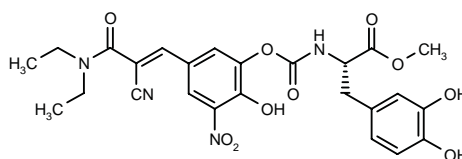
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TREATMENT OF EXTRAPYRAMIDAL MOVEMENT DISORDERS**316757**

N-[5-[(*E*)-2-Cyano-2-(*N,N*-diethylcarbamoyl)vinyl]-2-hydroxy-3-nitrophenoxy]carbonyl]-3-hydroxy-*L*-tyrosine methyl ester



C25 H26 N4 O10; Mol wt: 542.4984

ACTION – *L*-Dopa ester of entacapone, a codrug with relative stability to chemical hydrolysis but which is rapidly hydrolyzed to *L*-dopa and entacapone in liver homogenates. Potentially useful for the treatment of Parkinson's disease.

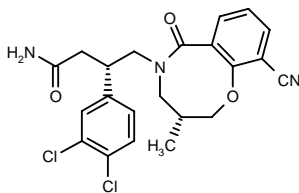
SOURCES – Finncover; University of Kuopio, Kuopio (FI).

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318874

4-[10-Cyano-3(*R*)-methyl-6-oxo-3,4,5,6-tetrahydro-2*H*-1,5-benzoxazocin-5-yl]-3(*S*)-(3,4-dichlorophenyl)butyramide



C22 H21 Cl2 N3 O3; Mol wt: 446.3319

ACTION – A representative compound from a series of cyclized benzamide derivatives with tachykinin NK₁ receptor-antagonist activity. Potentially useful for the treatment of depression, anxiety, eating disorders, stress disorders, bipolar disorder, drug abuse, schizophrenia, psychoses, movement disorders, cognitive disorders, aggressive behavior, obesity, emesis, rheumatoid arthritis, Alzheimer's disease, cancer, edema, allergic rhinitis, migraine, bladder hypermotility and urticaria.

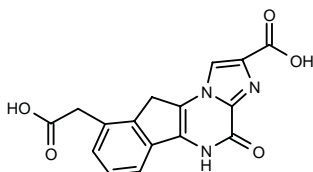
SOURCE – AstraZeneca.

REFERENCES

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NEUROLOGIC DRUGS**ANTIEPILEPTIC DRUGS****RPR-117824****295128**

9-(Carboxymethyl)-4-oxo-5,10-dihydro-4*H*-imidazo[1,2-*a*]-indeno[1,2-*e*]pyrazine-2-carboxylic acid



C16 H11 N3 O5; Mol wt: 325.2789

ACTION – Potent AMPA antagonist with high affinity for AMPA receptors and selectivity over NMDA receptors (IC₅₀ = 18 and 7200 nM, respectively). In functional studies, compound competitively inhibited the electrophysiological responses mediated by AMPA receptors expressed in *Xenopus* oocytes and in rat brain (IC₅₀ = 0.36 μM). It displayed anticonvulsant activity in several *in vivo* models including supramaximal electroshock seizures in mice (ED₅₀ = 0.83 mg/kg i.p.) and generalized

clonic seizures induced by chemoconvulsants including pentylenetetrazol, bicuculline and isoniazid (ED₅₀ = 1.5-1.7 mg/kg s.c.). In addition, it exhibited neuroprotective activity in a global ischemia model in gerbils and a focal ischemia model in rats, as well as in traumatic brain injury and spinal cord injury models in rats. Potentially useful for the treatment of epilepsy and stroke.

SOURCE – Aventis Pharma.

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1. Aloup, J.-C. et al. (Rhône-Poulenc Rorer SA) *5*H*,10*H*-Imidazo[1,2-*a*]indeno[1,2-*e*]pyrazine-4-one derivs., preparation thereof, intermediates thereof and drugs containing same*. EP 0880522, FR 2743366, JP 2000505073, US 5990108, WO 9725328.

2. Damour, D. et al. *Synthesis and potent anticonvulsant activities of 4-oxo-10*H*-imidazo[1,2-*a*]indeno[1,2-*e*]pyrazin-2-carboxylic acid AMPA antagonists*. 16th Int Symp Med Chem (Sept 18-22, Bologna) 2000, Abst PB-62.

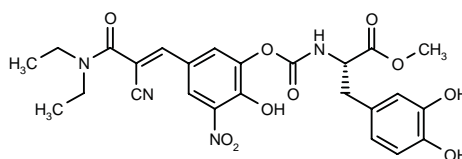
3. Mignani, S. et al. *9-Carboxymethyl-5*H*,10*H*-imidazo[1,2-*a*]indeno[1,2-*e*]pyrazin-4-one-2-carboxylic acid (RPR117824): Selective anticonvulsive and neuroprotective AMPA antagonist*. Bioorg Med Chem 2002, 10(5): 1627.

4. Mignani, S. et al. *Synthesis and pharmacological properties of 4-oxo-imidazo[1,2-*a*]indeno[1,2-*e*]pyrazin-2-carboxyl acid AMPA antagonists*. Soc Neurosci Abst 2000, 26(Part 1): Abst 42.11.

5. Pratt, J. et al. *Synthesis and potent anticonvulsant activities of 4-oxo-imidazo[1,2-*a*]indeno[1,2-*e*]pyrazin-8- and -9-carboxylic (acetic) acid AMPA antagonists*. Bioorg Med Chem Lett 2000, 10(24): 2749.

TREATMENT OF EXTRAPYRAMIDAL MOVEMENT DISORDERS**316757**

N-[5-[(*E*)-2-Cyano-2-(*N,N*-diethylcarbamoyl)vinyl]-2-hydroxy-3-nitrophenoxy-carbonyl]-3-hydroxy-*L*-tyrosine methyl ester



C25 H26 N4 O10; Mol wt: 542.4984

ACTION – *L*-Dopa ester of entacapone, a codrug with relative stability to chemical hydrolysis but which is rapidly hydrolyzed to *L*-dopa and entacapone in liver homogenates. Potentially useful for the treatment of Parkinson's disease.

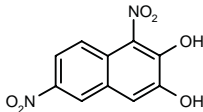
SOURCES – Finncover; University of Kuopio, Kuopio (FI).

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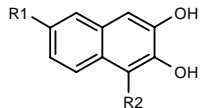
319297

1,6-Dinitronaphthalene-2,3-diol

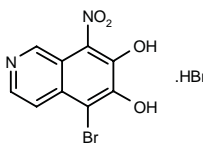


C10 H6 N2 O6; Mol wt: 250.1654

ACTION – Catechol *O*-methyltransferase (COMT) inhibitor (IC₅₀ = 12 nM), potentially useful for the treatment of Parkinson’s disease. Other exemplified naphthalene derivatives are:



Compound	R1	R2	Formula
319298	H	NO2	C ₁₀ H ₇ NO ₄
319299	COPh	NO2	C ₁₇ H ₁₁ NO ₅
319301	i-PrCO	NO2	C ₁₄ H ₁₃ NO ₅
319302	i-Bu	NO2	C ₁₄ H ₁₅ NO ₄
319303	CO2H	NO2	C ₁₁ H ₇ NO ₆
319304	H	CHO	C ₁₁ H ₈ O ₃
319305	COC6H13	NO2	C ₁₇ H ₁₉ NO ₅
319306	SO2N(Pr)2	NO2	C ₁₆ H ₂₀ N ₂ O ₆ S
319307	H	CN	C ₁₁ H ₇ NO ₂
319308	4-Me-1-Pip-CO	NO2	C ₁₇ H ₁₈ N ₂ O ₅



319309: C9 H5 Br N2 O4 . HBr

SOURCE – Orion Corporation.

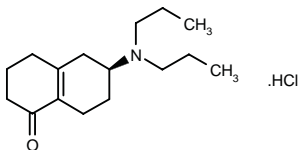
REFERENCES

1. Bäckström, R. et al. (Orion Corporation) *Derivs. of naphthalene with COMT inhibiting activity*. WO 0222551.

(S)-PD-148903

294729

(–)-6(*S*)-(Dipropylamino)-1,2,3,4,5,6,7,8-octahydro-naphthalen-1-one hydrochloride



C16 H27 N O . HCl; Mol wt: 285.8562

ACTION – Orally active prodrug of the potent mixed dopamine D1/D2 receptor agonist 5,6-di-OH-DPAT; it is rapidly converted to the active dopamine agonist and delivered enantioselectively into the CNS, as demonstrated in dialysis experiments in rats. The prodrug was effective in a rat model of Parkinson’s disease after oral administration.

SOURCE – Pfizer.

REFERENCES

1. Dijkstra, D. et al. (Pfizer Inc.) *Method for treating Parkinson’s disease by administering (–)-5-keto-2-N,N-di-N-propylamino-tetrahydrotetralin*. WO 0128977.

2. Johnson, S.J. et al. *Dihydro analogs of 5- and 7-hydroxy-2-aminotetralins; synthesis and dopaminergic activity*. 207th ACS Natl Meet (March 13-17, San Diego) 1994, Abst MEDI 175.

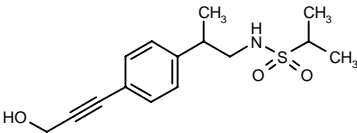
3. Venhuis, B.J. et al. *A new type of prodrug of catecholamines: An opportunity to improve the treatment of Parkinson’s disease*. J Med Chem 2002, 45(12): 2349.

4. Venhuis, B.J. et al. *Enone prodrugs of hydroxylated aminotetralins: PD148903, derivatives and analogs*. 16th Int Symp Med Chem (Sept 18-22, Bologna) 2000, Abst PB-135.

TREATMENT OF
COGNITION DISORDERS

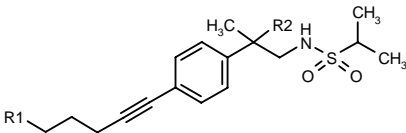
318377

N-[2-[4-(3-Hydroxy-1-propynyl)phenyl]propyl]propane-2-sulfonamide



C15 H21 N O3 S; Mol wt: 295.4009

ACTION – Glutamate receptor potentiator, considered to have potential in the treatment of a variety of neurological and psychiatric disorders including cognitive disorders such as Alzheimer’s disease, age-related dementia and age-induced memory impairment, movement disorders, reversal of drug-induced states, depression, attention deficit hyperactivity disorder, psychosis and stroke. Other specifically claimed acetylenic sulfonamide derivatives include the following:



Compound	R1	R2	Formula
318378	CH2OH	H	C ₁₈ H ₂₇ NO ₃ S
318379	CH2NHAc	H	C ₂₀ H ₃₀ N ₂ O ₃ S
318380	CH2NHCON(Me)2	H	C ₂₁ H ₃₃ N ₃ O ₃ S
318381	CH2OH	F	C ₁₈ H ₂₆ FNO ₃ S
318382	CH2OH	H	C ₁₈ H ₂₇ NO ₃ S
318383	NHAc	H	C ₁₉ H ₂₈ N ₂ O ₃ S
318384	i-PrCONH	H	C ₂₁ H ₃₂ N ₂ O ₃ S
318385	OH	F	C ₁₇ H ₂₄ FNO ₃ S

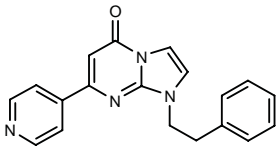
SOURCE – Lilly.

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1. Bender, D.M. et al. (Eli Lilly and Company) *Acetylenic sulfonamide derivs*. WO 0218329.

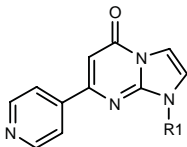
318387

1-(2-Phenylethyl)-7-(4-pyridyl)imidazo[1,2-*a*]pyrimidin-5(1*H*)-one

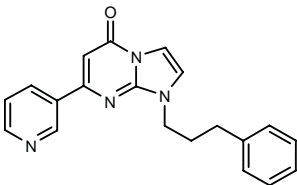


C19 H16 N4 O; Mol wt: 316.3624

ACTION – Glycogen synthase kinase-3β (GSK-3β) inhibitor, potentially useful for the treatment of neurodegenerative diseases including Alzheimer's disease, Parkinson's disease, vascular dementia, acute stroke, brain and spinal cord trauma and peripheral neuropathies. Further applications include retinopathies, glaucoma, type 2 diabetes, obesity, manic–depressive disorder, schizophrenia, alopecia and cancer. Other exemplified compounds include the following:



Compound	R1	Formula
318388	4-MeO-Ph(CH2)3	C ₂₁ H ₂₀ N ₄ O ₂
318389	CH2CH2SPh	C ₁₉ H ₁₆ N ₄ OS
318391	CH=CHCH2CF3	C ₁₅ H ₁₁ F ₃ N ₄ O
318392	3-Pyr-(CH2)3	C ₁₉ H ₁₇ N ₅ O
318393	2-Naph-COCH2	C ₂₃ H ₁₆ N ₄ O ₂
318394	4-Cl-PhCOCH2	C ₁₉ H ₁₃ ClN ₄ O ₂
318395	2-Naph-CH(OH)CH2	C ₂₃ H ₁₈ N ₄ O ₂



318390: C20 H18 N4 O

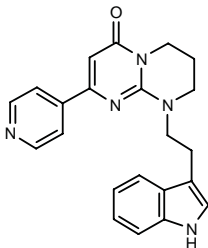
SOURCES – Mitsubishi Pharma; Sanofi-Synthélabo.

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1. Lohead, A. et al. (Sanofi-Synthélabo;Mitsubishi-Tokyo Pharmaceuticals, Inc.) 1-(Alkyl), 1-[(heteroaryl)alkyl] and 1-[(aryl)alkyl]-7-pyridinyl-imidazo[1,2-*a*]pyrimidin-5(1*H*)-one derivs. EP 1184384, WO 0218385.

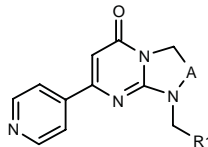
318400

9-[2-(1*H*-Indol-3-yl)ethyl]-2-(4-pyridyl)-6,7,8,9-tetrahydro-4*H*-pyrimido[1,2-*a*]pyrimidin-4-one



C22 H21 N5 O; Mol wt: 371.4419

ACTION – Glycogen synthase kinase-3β (GSK-3β) inhibitor, potentially useful for the treatment of neurodegenerative diseases including Alzheimer's disease, Parkinson's disease, vascular dementia, acute stroke, brain and spinal cord trauma and peripheral neuropathies. Further applications include retinopathies, glaucoma, type 2 diabetes, obesity, manic–depressive disorder, schizophrenia, alopecia and cancer. Other exemplified compounds include the following:



Compound	R1	A	Formula
318401	2-MeO-PhOCH2	-CH2CH2-	C ₂₁ H ₂₂ N ₄ O ₃
318402	4-Cl-PhCH2CH2	-CH2CH2-	C ₂₁ H ₂₁ ClN ₄ O
318403	CH2SMe	-CH2CH2-	C ₁₈ H ₁₈ N ₄ OS
318404	cyclohexyl-CH2CH2	-CH2CH2-	C ₂₁ H ₂₈ N ₄ O
318405	4-Me-PhCO	-CH2CH2-	C ₂₁ H ₂₀ N ₄ O ₂
318408	cyclohexyl-CH2	-CH2-	C ₁₉ H ₂₄ N ₄ O
318409	3-MeO-PhCO	-CH2-	C ₂₀ H ₁₈ N ₄ O ₃

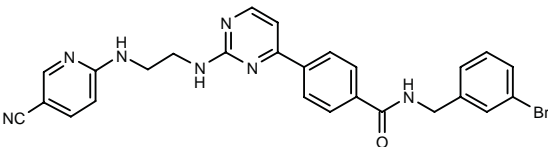
SOURCES – Mitsubishi Pharma; Sanofi-Synthélabo.

REFERENCES

1. Almario Garcia, A. et al. (Sanofi-Synthélabo;Mitsubishi-Tokyo Pharmaceuticals, Inc.) 2-Pyridinyl-6,7,8,9-tetrahydropyrimido[1,2-*a*]pyrimidin-4-one and 7-pyridinyl-2,3-dihydroimidazo[1,2-*a*]pyrimidin-5(1*H*)-one derivs. EP 1184383, EP 1184385, WO 0218386.

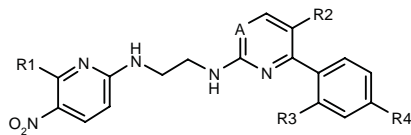
319083

N-(3-Bromobenzyl)-4-[2-[2-(5-cyanopyridin-2-ylamino)-ethylamino]pyrimidin-4-yl]benzamide

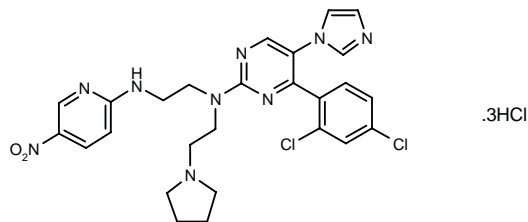


C26 H22 Br N7 O; Mol wt: 528.4118

ACTION – Glycogen synthase kinase (GSK-3) inhibitor for use in the treatment of diabetes, Alzheimer’s disease and other neurodegenerative disorders, obesity, atherosclerosis, essential hypertension, polycystic ovary syndrome, syndrome X, ischemia, traumatic brain injury, bipolar disorder and cancer. Other exemplified compounds include the following:



Compound	R1	R2	R3	R4	A	Formula
319084	H	CO2Et	H	4-morpholinyl	N	C ₂₄ H ₂₇ N ₇ O ₅
319085	H	Et	Cl	Cl	N	C ₁₉ H ₁₈ Cl ₂ N ₆ O ₂
319086	NH2	3-(4-morpholinyl)-2,5-dioxo-1-pyrrolidinyl	Cl	Cl	N	C ₂₅ H ₂₆ Cl ₂ N ₉ O ₅
319088	NH2	1-imidazolyl	Cl	Cl	N	C ₂₀ H ₁₇ Cl ₂ N ₉ O ₂
319089	H	2-imidazolyl	Cl	H	N	C ₂₀ H ₁₇ ClN ₈ O ₂
319090	NH2	2-imidazolyl	CF3	F	N	C ₂₁ H ₁₇ F ₄ N ₉ O ₂
319091	NH2	2-imidazolyl	Cl	Cl	CH	C ₂₁ H ₁₈ Cl ₂ N ₈ O ₂



319092: C26 H27 Cl2 N9 O2 . 3HCl

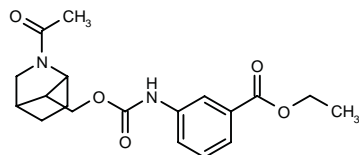
SOURCE – Chiron.

REFERENCES

1. Nuss, J.M. et al. (Chiron Corp.) *Inhibitors of glycogen synthase kinase 3*. WO 0220495.

319273

3-(2-Acetyl-2-azabicyclo[2.2.1]hept-7-ylmethoxycarbonylamino)benzoic acid ethyl ester



C19 H24 N2 O5; Mol wt: 360.4076

ACTION – A representative compound from a series of 2-azabicyclo[2.2.1]hept-7-ylmethanol derivatives with the ability to activate nicotinic acetylcholine receptors. Potentially useful for the treatment of schizophrenia, Alzheimer’s disease, Parkinson’s disease, Tourette’s syndrome, age-dependent memory impairment, drug abuse and stroke.

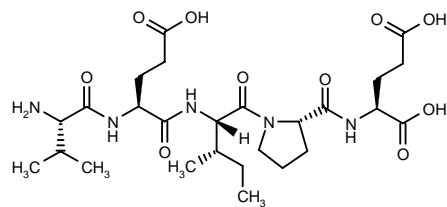
SOURCE – Merck KGaA.

REFERENCES

1. Schiemann, K. and Leibrock, J. (Merck Patent GmbH) *(2-Azabicyclo[2.2.1]hept-7-yl)methanol derivs. as nicotinic acetylcholine receptor agonists*. DE 10044905, WO 0222578.

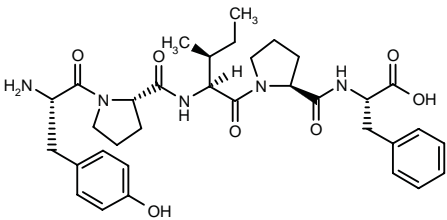
319443

L-Valyl-L-glutamyl-L-isoleucyl-L-prolyl-L-glutamic acid



C26 H43 N5 O10; Mol wt: 585.6507

ACTION – A short peptide with the ability to inhibit prolyl endopeptidase (prolyl oligopeptidase; IC₅₀ = 17.0 μM). Potentially useful for the treatment of dementia. Another



319444: C34 H45 N5 O7

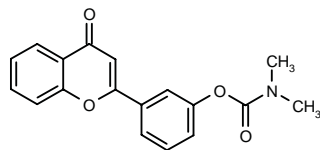
SOURCE – Mercian.

REFERENCES

1. Yanai, T. and Sato, M. (Mercian Corp.) *Prolyl endopeptidase inhibiting peptide*. JP 2002080497.

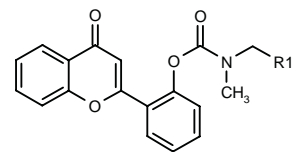
319446

N,N-Dimethylcarbamic acid 3-(4-oxo-4H-1-benzopyran-2-yl)phenyl ester



C18 H15 N O4; Mol wt: 309.3195

ACTION – Dual-acting agent that combines both acetylcholinesterase (AChE)-inhibitory (IC₅₀ = 1.4 μM) and antioxidant activity. Potentially useful for the treatment of Alzheimer’s disease. Other exemplified flavone derivatives are:



Compound	R1	Formula
319448	H	C ₁₈ H ₁₅ NO ₄
319450	Me	C ₁₉ H ₁₇ NO ₄

SOURCES – Biogal; Teva.

REFERENCES

1. Ildiko, M.B. et al. (Teva Pharmaceutical Industries Ltd.; Teva Pharmaceuticals USA, Inc.) *N-Disubst. carbamoyloxy flavones*. WO 0224676.

2. Ildiko, M. et al. (Biogal Pharmaceutical Co., Ltd.; Teva Pharmaceuticals USA, Inc.) *N-Disubst. carbamoyl-oxyflavones*. WO 0224677.

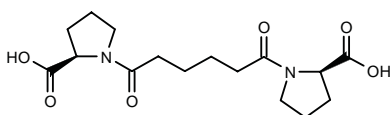
RO-63-8695

320000

1-[6-[2(*R*)-Carboxy-1-pyrrolidiny]-6-oxohexanoyl]pyrrolidine-2(*R*)-carboxylic acid

1,1'-(1,6-Dioxo-1,6-hexanediyl)bis(*D*-proline)

CPHPC



C16 H24 N2 O6; Mol wt: 340.3736

ACTION – Selective inhibitor of serum amyloid P (SAP) binding to β -amyloid fibrils ($IC_{50} = 0.9 \mu M$), potentially useful for the treatment of both systemic amyloidosis and diseases associated with local amyloid including Alzheimer's disease and type 2 diabetes. In mice compound was not metabolized and was very rapidly excreted; following various routes of administration (i.v., s.c., i.p., p.o.), it was found to inhibit the uptake of human SAP into amyloid deposits, deplete SAP from amyloid deposits and rapidly clear SAP from the circulation via the liver. In a transgenic mouse model of amyloidosis in which human SAP is expressed instead of mouse SAP, compound significantly reduced amyloid deposition and burden. No adverse effects were seen in rats and dogs treated for 28 days with i.v. doses of up to 400 mg/kg. A preliminary clinical study in patients with systemic amyloidosis showed that compound rapidly depleted circulating SAP in all subjects, with almost complete clearance at doses of 0.25-6 mg/kg/day by i.v. infusion. In a subsequent study in patients with systemic amyloidosis, many with end-stage disease, doses of 30-40 mg/kg/day s.c. or i.v. for up to 9.5 months markedly reduced plasma SAP levels and most of these patients were clinically stable during treatment. Long-term studies in systemic amyloidosis patients are currently under way.

SOURCE – Roche.

REFERENCES

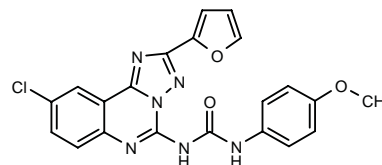
1. Hertel, C. et al. (F. Hoffmann-La Roche AG) *D-Proline derivs*. CA 2252163, EP 0915088, JP 1999209343, US 6262089.

2. Pepys, M.B. et al. *Targeted pharmacological depletion of serum amyloid P component for treatment of human amyloidosis*. Nature 2002, 417(6886): 254.

TREATMENT OF CEREBROVASCULAR DISEASES

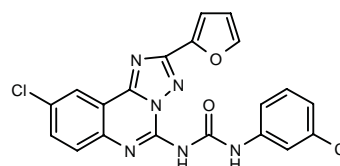
318756

*N*¹-[9-Chloro-2-(2-furyl)-[1,2,4]triazolo[1,5-*c*]quinazolin-5-yl]-*N*³-(4-methoxyphenyl)urea



C21 H15 Cl N6 O3; Mol wt: 434.8415

ACTION – Adenosine A_3 receptor modulator with high affinity for adenosine A_3 receptors and 43-, 50- and 158-fold selectivity over A_1 , A_{2A} and A_{2B} receptor subtypes. Potentially useful for the treatment of cardiac hypoxia and cerebral ischemia, as well as hypertension, inflammation, allergies and mast cell degranulation. Another exemplified compound is:



318757: C20 H12 Cl2 N6 O2

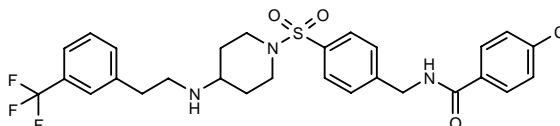
SOURCE – King Pharmaceuticals.

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1. Baraldi, P.G. (King Pharmaceuticals, Inc.) *Adenosine, A_3 receptor modulators*. US 6358964.

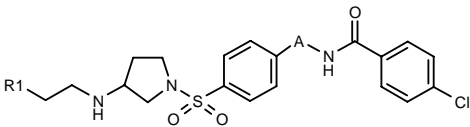
318662

4-Chloro-*N*-[4-[4-[2-[3-(trifluoromethyl)phenyl]ethyl]amino]piperidin-1-ylsulfonyl]benzyl]benzamide

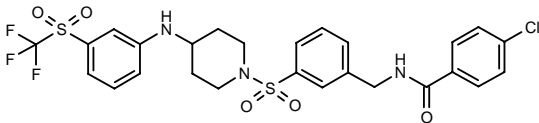


C28 H29 Cl F3 N3 O3 S; Mol wt: 580.0681

ACTION – Inhibitor of c-Jun *N*-terminal kinases (JNKs), especially JNK2 and JNK3, considered to have potential in the treatment of neuronal disorders including epilepsy, Alzheimer's disease, Huntington's disease, Parkinson's disease, retinal diseases, spinal cord injury, multiple sclerosis, head trauma and ischemia, as well as autoimmune disorders such as inflammatory bowel disease, rheumatoid arthritis, asthma, septic shock and transplant rejection, cancer, cardiovascular disorders including stroke, arteriosclerosis, myocardial infarction and myocardial reperfusion injury, heart and kidney ischemia and renal failure. Other exemplified benzene-sulfonamide derivatives are:



Compound	R1	A	Formula
318664	Bu	bond	C ₂₃ H ₃₀ ClN ₃ O ₃ S
318667	3-CF ₃ -Ph	-CH ₂ -	C ₂₇ H ₂₇ ClF ₃ N ₃ O ₃ S



318663: C₂₆ H₂₅ Cl F₃ N₃ O₅ S₂

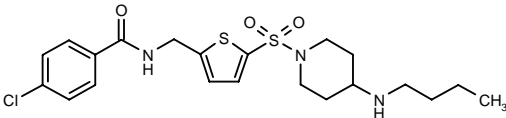
SOURCE – Applied Research Systems.

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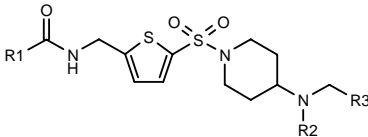
318867

N-[5-[4-(Butylamino)piperidin-1-ylsulfonyl]thien-2-yl-methyl]-4-chlorobenzamide



C₂₁ H₂₈ Cl N₃ O₃ S₂; Mol wt: 470.0552

ACTION – An inhibitor of c-Jun kinases (JNK), particularly JNK2 and/or JNK3. Compound was able to inhibit PMA- and ionomycin-stimulated IL-2 production in Jurkat cells with an IC₅₀ < 800 nM. It also demonstrated *in vivo* activity in a gerbil model of acute ischemic stroke (64% inhibition of ischemia at 80 mg/kg). Potentially useful for the treatment of neuronal disorders including epilepsy, Alzheimer’s disease, Huntington’s disease, Parkinson’s disease, retinal disease, head and spinal cord injury, multiple sclerosis and ischemia, and autoimmune disorders such as inflammatory bowel disease, rheumatoid arthritis, asthma, septic shock and transplant rejection. Other exemplified sulfonamide derivatives are:



Compound	R1	R2	R3	Formula
318868	3-MeO-Ph	H	4-CF ₃ -Ph	C ₂₆ H ₂₈ F ₃ N ₃ O ₄ S ₂
318869	4-Cl-Ph	H	C ₅ H ₁₁	C ₂₃ H ₃₂ ClN ₃ O ₃ S ₂
318870	3-MeO-Ph	H	4-(CF ₃ SO ₂)-Ph	C ₂₆ H ₂₈ F ₃ N ₃ O ₆ S ₃
318871	4-Cl-Ph	C ₆ H ₁₃	H	C ₂₄ H ₃₄ ClN ₃ O ₃ S ₂
318873	2-oxo-1,2-dihydro-3-Pyr	H	4-CF ₃ -Ph	C ₂₄ H ₂₅ F ₃ N ₄ O ₄ S ₂

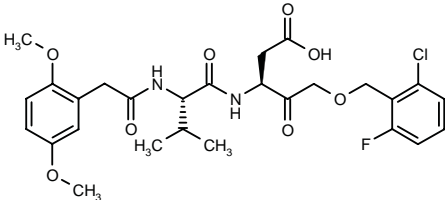
SOURCE – Applied Research Systems.

REFERENCES

1. Halazy, S. et al. (Applied Research Systems ARS Holdings NV) *Pharmaceutically active sulfonamide derivs. bearing both lipophilic and ionisable moieties as inhibitors of protein Junkinases*. EP 1193268, WO 0226733.

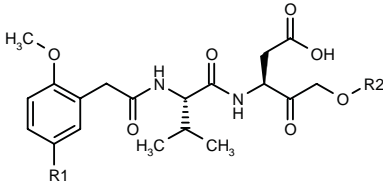
319024

5-(2-Chloro-6-fluorobenzyloxy)-3(*S*)-[*N*-[2-(2,5-dimethoxyphenyl)acetyl]-L-valylamino]-4-oxopentanoic acid



C₂₇ H₃₂ Cl F N₂ O₈; Mol wt: 567.0068

ACTION – Caspase 3 inhibitor with potential in the treatment of cardiac and cerebral ischemia–reperfusion injury, cerebral and spinal cord trauma, organ damage during transplantation, neurodegenerative diseases such as Alzheimer’s disease, Parkinson’s disease and Down’s syndrome, spinal muscular atrophy, multiple sclerosis, immunodeficiency, HIV infection, diabetes, alopecia, aging and sepsis. Other specifically claimed compounds are:



Compound	R1	R2	Formula
319025	3-Me-1,2,4-oxadiazol-5-yl	4-(PhCH ₂ O)-Ph	C ₃₅ H ₃₈ N ₄ O ₉
319026	3-Me-1,2,4-oxadiazol-5-yl	4-Br-2-F-Ph	C ₂₈ H ₃₀ BrFN ₄ O ₈
319027	3-Me-1,2,4-oxadiazol-5-yl	2-(PhO)-PhCO	C ₃₅ H ₃₈ N ₄ O ₁₀
319029	3-Me-1,2,4-oxadiazol-5-yl	1-isoquinolinylnyl-CO	C ₃₂ H ₃₃ N ₅ O ₉
319030	Ac	8-CF ₃ -4-quinolinylnyl	C ₃₁ H ₃₂ F ₃ N ₃ O ₈
319031	Ac	3-Pyr	C ₂₆ H ₃₁ N ₃ O ₈
319032	Ac	2-t-Bu-Ph	C ₃₁ H ₄₀ N ₂ O ₈
319033	Ac	2-F-5-CF ₃ -Ph	C ₂₈ H ₃₀ F ₄ N ₂ O ₈

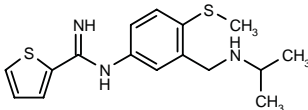
SOURCE – Merck Frosst.

REFERENCES

1. Han, Y. et al. (Merck Frosst Canada Inc.) *γ-Ketoacid dipeptides as inhibitors of caspase-3*. WO 0220465.

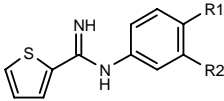
319122

N-[3-(Isopropylaminomethyl)-4-(methylsulfonyl)phenyl]-thiophene-2-carboxamide



C₁₆ H₂₁ N₃ S₂; Mol wt: 319.4949

ACTION – Nitric oxide synthase (NOS) inhibitor, particularly active against the neuronal isoform of the enzyme. Potentially useful for the treatment of stroke, pain, migraine, schizophrenia and Parkinson’s disease. Other specifically claimed amidine derivatives include the following:



Compound	R1	R2	Formula
319123	SMe	NHCH2CH2CF3	C15H16F3N3S2
319124	SMe	CH2NHCH2CH2OH	C15H19N3OS2
319125	SOMe	CH2N(Me)CH2CH2OH	C16H21N3O2S2
319126	SMe	CH2NHEt	C15H19N3S2
319127	SMe	CH2NH2	C13H15N3S2
319128	SMe	CH2NHPr	C16H21N3S2
319129	SMe	CH2NH(CH2)3OH	C16H21N3OS2
319130	SMe	CH2N[(CH2)3Ph]2	C31H35N3S2

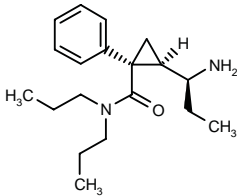
SOURCE – AstraZeneca.

REFERENCES

1. Chen, D. et al. (AstraZeneca AB) *Amidine derivs. which are inhibitors of nitric oxide synthase*. WO 0220511.

319289

(1*S*,2*R*)-2-[1(*S*)-Aminopropyl]-1-phenyl-*N,N*-dipropylcyclopropanecarboxamide



C19 H30 N2 O; Mol wt: 302.4590

ACTION – Potent and selective NMDA receptor antagonist with nanomolar affinity for NMDA receptors (IC₅₀ = 130 nM) and able to reduce the NMDA receptor-mediated induction of long-term potentiation (LTP) in rat hippocampus. Potentially useful for the treatment of acute and chronic neurodegenerative disorders.

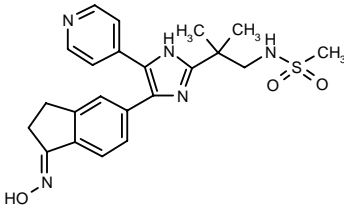
SOURCE – Asahi Kasei.

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1. Kazuta, Y. et al. *Synthesis of (1*S*,2*R*)-1-phenyl-2-[(*S*)-1-aminopropyl]-*N,N*-diethylcyclopropanecarboxamide (PPDC) derivatives modified at the carbamoyl moiety as a new class of NMDA receptor antagonists*. Bioorg Med Chem 2002, 10(6): 1777.

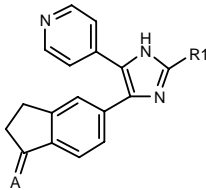
319453

N-[2-[4-[1-(Hydroxyimino)-2,3-dihydro-1*H*-inden-5-yl]-5-(4-pyridyl)-1*H*-imidazol-2-yl]-2-methylpropyl]methane-sulfonamide



C22 H25 N5 O3 S; Mol wt: 439.5375

ACTION – An inhibitor of Raf kinases, in particular B-Raf kinase. Potentially useful for the treatment of cancer, neurotraumatic disorders, chronic neurodegeneration, pain, migraine and cardiac hypertrophy. Other exemplified imidazole derivatives are:



Compound	R1	A	Formula
319454	4-Pip	N(OH)	C22H23N5O
319455	1-(3-furyl-CH2)-4-Pip	N(OH)	C27H27N5O2
319456	1-Pip-CH2	N(OH)	C23H25N5O
319457	4-(2-pyrazinyl)-1-Piz-CH2	N(OH)	C26H26N8O
319458	4-[N(Me)2(CH2)3O]-Ph	O	C28H28N4O2
319459	4-[N(Me)2CH2CH2O]-Ph	O	C27H26N4O2
319461	3-Pyr	O	C22H16N4O
319462	Ph	O	C23H17N3O

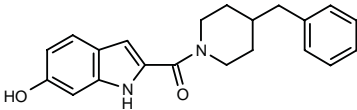
SOURCE – GlaxoSmithKline.

REFERENCES

1. Dean, D.K. et al. (GlaxoSmithKline plc) *Imidazole derivs. as Raf kinase inhibitors*. WO 0224680.

319535

1-(4-Benzylpiperidin-1-yl)-1-(6-hydroxy-1*H*-indol-2-yl)-methanone



C21 H22 N2 O2; Mol wt: 334.4168

ACTION – NMDA receptor antagonist displaying an IC_{50} of 0.018 μ M at NMDA receptors and > 2,000-fold selectivity for the NR2B subunit. Potentially useful for the treatment of neurodegenerative disorders such as stroke, Alzheimer's disease, Parkinson's disease, Huntington's disease and spinal cord trauma, epilepsy, anxiety, depression, muscular spasm, multiinfarct dementia, brain injury, pain, migraine, HIV-related neuronal injury, hypoglycemia, amyotrophic lateral sclerosis, macular degeneration, retinitis, asthma, bacterial and viral infections, drug abuse, psychosis and urinary incontinence.

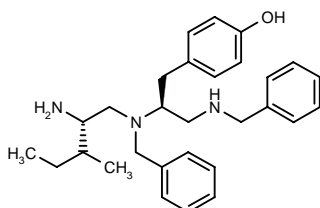
SOURCE – Gedeon Richter.

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319672

4-[2(S)-[N-[2(S)-Amino-3-methylpentyl]-N-benzylamino]-3-(benzylamino)propyl]phenol



C29 H39 N3 O; Mol wt: 445.6471

ACTION – NMDA receptor channel blocker able to protect rat hippocampal neurons from NMDA-induced cell death by 83% at 10 μ M. Compound was shown to exert its neuroprotective action through selective blockade of NMDA receptors relative to non-NMDA receptors such as GluR1 (AMPA) receptors. Potentially useful as a neuroprotectant in the treatment of ischemic stroke.

SOURCE – University of California, Oakland, CA (US).

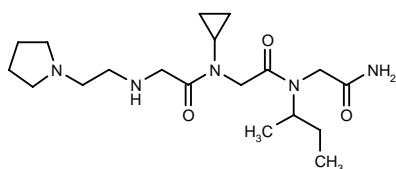
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DD-612

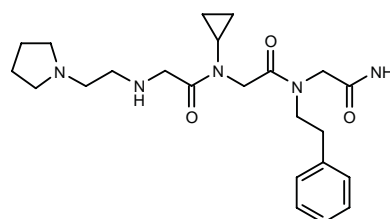
318840

N-[2-(1-Pyrrolidinyl)ethyl]-glycyl-N-cyclopropyl-glycyl-N²-(1-methylpropyl)glycinamide



C19 H35 N5 O3; Mol wt: 381.5175

ACTION – Neuroprotective agent able to protect primary cultures of cerebellar neurons from glutamate-induced neuronal death (IC_{50} = 8 μ M) without blocking the glutamate NMDA receptor, attenuating the glutamate-induced increase in Ca^{2+} or affecting the glutamate–nitric oxide cGMP pathway. *In vivo*, it protected mice from death induced by ammonia and mediated by NMDA receptors; 100% survival was seen at the dose of 50 μ g/g i.p. In a rat model of cerebral ischemia, the dose of 50 μ g/g i.p. reduced infarct volume by 82% and caspase 3 activation in the striatum by 74%, indicating inhibition of apoptotic neuronal death. Although its cellular target remains to be identified, the compound may have reduced side effects compared to NMDA antagonists and potential in the treatment of acute and chronic neurodegenerative disorders. Another related trialkylglycine is:



DD-6110 [318842]: C23 H35 N5 O3

SOURCE – DiverDrugs.

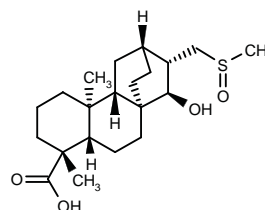
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2. Montoliu, C. et al. *Prevention of in vivo excitotoxicity by a family of trialkylglycines, a novel class of neuroprotectants*. J Pharmacol Exp Ther 2002, 301(1): 29.

SEROFENDIC ACID

317674

(4 β ,8 α ,10 α ,15 β)-15-Hydroxy-17-(methylsulfinyl)atisan-18-oic acid



C21 H34 O4 S; Mol wt: 382.5616

ACTION – Neuroprotective agent, a lipophilic diterpenoid isolated from fetal calf serum and proven to protect rat cerebral cortical cultures against nitric oxide (NO)-induced cell death (at 10 μ M) and glutamate-induced neurotoxicity (at 100 nM). This neuroprotective effect did not appear to be mediated by inhibition of glutamate receptor channels, nor by scavenging of NO radicals, but appeared to be due to inhibition of hydroxyl radical generation. Potentially useful for the treatment of stroke, Alzheimer's disease, Huntington's disease and Parkinson's disease.

SOURCE – Eisai.

REFERENCES

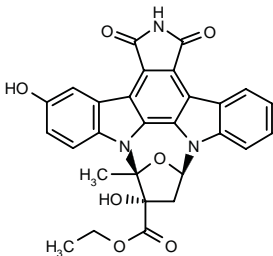
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MISCELLANEOUS NEUROLOGIC DRUGS

(+)-INDOCARBAZOSTATIN^{1,3-5}

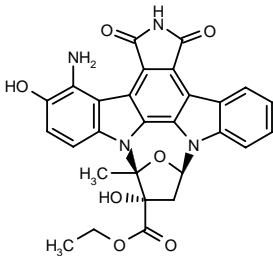
282034

5,10(*S*)-Dihydroxy-1,3-dioxo-9(*S*)-methyl-9,12(*R*)-epoxy-2,3,9,10,11,12-hexahydro-1*H*-diindolo[1,2,3-*fg*:3',2',1'-*kl*]-pyrrolo[3,4-*l*][1,6]benzodiazocine-10-carboxylic acid ethyl ester



C28 H21 N3 O7; Mol wt: 511.4879

ACTION – Indolocarbazole antibiotic extracted from the culture broth of *Streptomyces* sp. TA-0403, an inhibitor of nerve growth factor (NGF)-induced neuronal differentiation in rat pheochromocytoma PC-12 cells (MEC = 6 nM) that also exhibited inhibitory activity against protein kinase C (PKC; IC₅₀ = 2.0 nM). Compound did not exhibit cytotoxicity against PC-12 cells at concentrations up to 9-fold higher than its MEC. Potentially useful for the treatment of neuropathies such as intractable temporal lobe epilepsy and Huntington’s disease. Another related compound is:



(–)-Indocarbazostatin B [318930]²⁻⁴: C28 H22 N4 O7

SOURCES – Taisho; Toyama Medical and Pharmaceutical University, Toyama (JP).

REFERENCES

1. Ikukata, M. and Matsuura, N. *Indocarbazostatin.* JP 2000229979.
2. Matsuura, N. and Ikukata, M. *Indocarbazostatin B.* JP 2002037790.
3. Matsuura, N. et al. *Indocarbazostatin and indocarbazostatin B, novel inhibitors of NGF-induced neuronal differentiation in PC12 cells. I. Screening, taxonomy, fermentation and biological activities.* J Antibiot 2002, 55(4): 355.

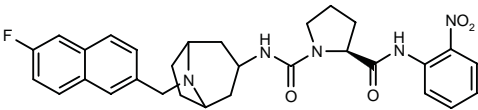
4. Tamehiro, N. et al. *Indocarbazostatin and indocarbazostatin B, novel inhibitors of NGF-induced neuronal differentiation in PC12 cells. II. Isolation, physicochemical properties and structural elucidation.* J Antibiot 2002, 55(4): 363.
5. Ubukata, M. *Indocarbazostatin, a novel inhibitor of NGF-induced neurite outgrowth from rat pheochromocytoma PC12 cells.* J Antibiot 1999, 52(10): 921.

RESPIRATORY DRUGS

ASTHMA THERAPY

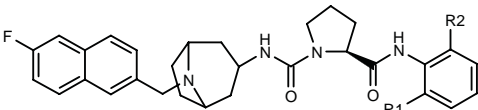
318761

1-[*N*-[8-(6-Fluoronaphthalen-2-yl)methyl]-8-azabicyclo[3.2.1]oct-3-yl]carbamoyl]-*N*-(2-nitrophenyl)-L-prolinamide



C30 H32 F N5 O4; Mol wt: 545.6118

ACTION – Chemokine CCR3 receptor antagonist (IC₅₀ = 0.45-0.001 μM) shown to inhibit eotaxin-induced degranulation of human peripheral blood eosinophils (IC₅₀ = 0.50-21 nM). Potentially useful for the treatment of inflammatory, allergic and autoimmune disorders including asthma, allergic rhinitis, sinusitis, rheumatoid arthritis, allergic conjunctivitis, atopic dermatitis, ulcerative colitis and Crohn’s disease, and also HIV infection, encephalitis and dementia related therewith. Other exemplified cyclic amine derivatives are:



Compound	R1	R2	Formula
318763	H	CF3	C ₃₁ H ₃₂ F ₄ N ₄ O ₂
318765	Cl	Cl	C ₃₀ H ₃₁ Cl ₂ FN ₄ O ₂
318767	H	CN	C ₃₁ H ₃₂ FN ₅ O ₂

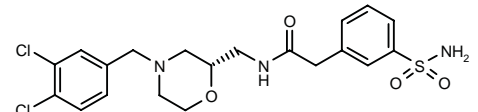
SOURCES – Toray; Yamanouchi.

REFERENCES

1. Morihira, K. et al. (Yamanouchi Pharmaceutical Co., Ltd.;Toray Industries, Inc.) *Cyclic amine derivs.* WO 0218335.

318897

N-[4-(3,4-Dichlorobenzyl)morpholin-2(*S*)-ylmethyl]-2-(3-sulfamoylphenyl)acetamide



C20 H23 Cl2 N3 O4 S; Mol wt: 472.3907

SOURCE – Eisai.

REFERENCES

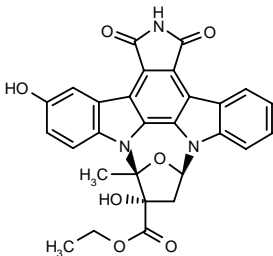
1. Kume, T. et al. *Isolation of a diterpenoid substance with potent neuroprotective activity from fetal calf serum.* Proc Natl Acad Sci USA 2002, 99(5): 3288.

MISCELLANEOUS NEUROLOGIC DRUGS

(+)-INDOCARBAZOSTATIN^{1,3-5}

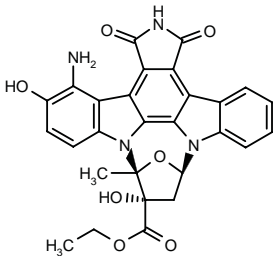
282034

5,10(*S*)-Dihydroxy-1,3-dioxo-9(*S*)-methyl-9,12(*R*)-epoxy-2,3,9,10,11,12-hexahydro-1*H*-diindolo[1,2,3-*fg*:3',2',1'-*kl*]-pyrrolo[3,4-*l*][1,6]benzodiazocine-10-carboxylic acid ethyl ester



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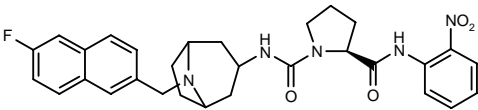
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5. Ubukata, M. *Indocarbazostatin, a novel inhibitor of NGF-induced neurite outgrowth from rat pheochromocytoma PC12 cells.* J Antibiot 1999, 52(10): 921.

RESPIRATORY DRUGS

ASTHMA THERAPY

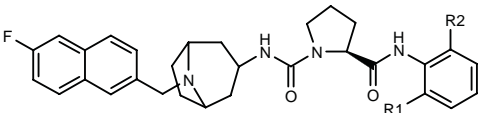
318761

1-[*N*-[8-(6-Fluoronaphthalen-2-yl)methyl]-8-azabicyclo[3.2.1]oct-3-yl]carbamoyl]-*N*-(2-nitrophenyl)-L-prolinamide



C30 H32 F N5 O4; Mol wt: 545.6118

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Compound	R1	R2	Formula
318763	H	CF3	C ₃₁ H ₃₂ F ₄ N ₄ O ₂
318765	Cl	Cl	C ₃₀ H ₃₁ Cl ₂ FN ₄ O ₂
318767	H	CN	C ₃₁ H ₃₂ FN ₅ O ₂

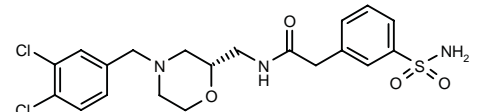
SOURCES – Toray; Yamanouchi.

REFERENCES

1. Morihira, K. et al. (Yamanouchi Pharmaceutical Co., Ltd.;Toray Industries, Inc.) *Cyclic amine derivs.* WO 0218335.

318897

N-[4-(3,4-Dichlorobenzyl)morpholin-2(*S*)-ylmethyl]-2-(3-sulfamoylphenyl)acetamide



C20 H23 Cl2 N3 O4 S; Mol wt: 472.3907

ACTION – Chemokine CCR3 receptor antagonist with antiinflammatory properties. Potentially useful for the treatment of allergic diseases, particularly bronchial asthma, allergic rhinitis and atopic dermatitis.

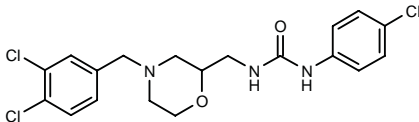
SOURCE – GlaxoSmithKline.

REFERENCES

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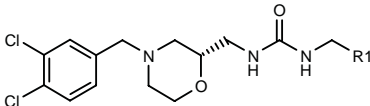
318898

N-(4-Chlorophenyl)-*N'*-[4-(3,4-dichlorobenzyl)morpholin-2-ylmethyl]urea



C19 H20 Cl3 N3 O2; Mol wt: 428.7450

ACTION – Chemokine CCR3 receptor antagonist with antiinflammatory properties. Compound was shown to inhibit lung eosinophilia and bronchial hyperreactivity in ovalbumin-sensitized guinea pigs. Potentially useful for the treatment of allergic diseases, particularly bronchial asthma, allergic rhinitis and atopic dermatitis. Other specifically claimed compounds are:



Compound	R1	Formula
318899	4-(NH2CO)-Ph	C ₂₁ H ₂₄ Cl ₂ N ₄ O ₃
318900	2-Me-5-tetrazolyl	C ₁₆ H ₂₁ Cl ₂ N ₇ O ₂
318901	4-(MeNHCO)-Ph	C ₂₂ H ₂₆ Cl ₂ N ₄ O ₃

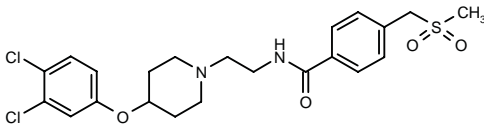
SOURCE – GlaxoSmithKline.

REFERENCES

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matory diseases.* WO 0226723.

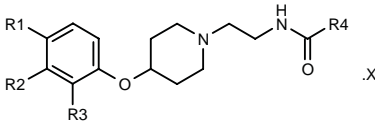
319073

N-[2-[4-(3,4-Dichlorophenoxy)piperidin-1-yl]ethyl]-4-(methylsulfonylmethyl)benzamide



C22 H26 Cl2 N2 O4 S; Mol wt: 485.4294

ACTION– Agent that acts as a chemokine CCR3 receptor modulator and a histamine H₁ receptor antagonist. Potentially useful for the treatment of autoimmune, inflammatory, proliferative and allergic conditions, particularly asthma and rhinitis. Other exemplified piperidine derivatives are:



Compound	R1	R2	R3	R4	X	Formula
319075	Cl	Cl	H	3-OH-Ph		C ₂₀ H ₂₂ Cl ₂ N ₂ O ₃
319076	Cl	Cl	H	3-(MeNHSO ₂)-Ph	acetate	C ₂₁ H ₂₅ Cl ₂ N ₃ O ₄ S .C ₂ H ₄ O ₂
319079	Cl	Cl	H	5-(1-pyrrolidinyl)- -2H-tetrazol-2-yl-CH ₂		C ₂₀ H ₂₇ Cl ₂ N ₇ O ₂
319080	Cl	Cl	H	imidazo[1,2-a]pyridin-2-yl		C ₂₁ H ₂₂ Cl ₂ N ₄ O ₂
319081	Cl	Me	Cl	5-(MeSO ₂)-2-thienyl		C ₂₀ H ₂₄ Cl ₂ N ₂ O ₄ S ₂
319082	F	F	H	4-Cl-3-(NH ₂ SO ₂)-Ph		C ₂₀ H ₂₂ ClF ₂ N ₃ O ₄ S

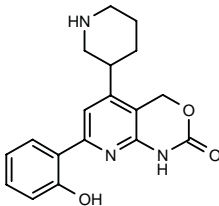
SOURCE – AstraZeneca.

REFERENCES

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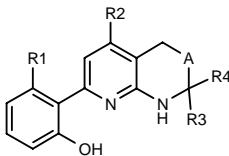
319486

7-(2-Hydroxyphenyl)-5-(3-piperidinyl)-2,4-dihydro-1*H*-pyrido[2,3-*d*][1,3]oxazin-2-one

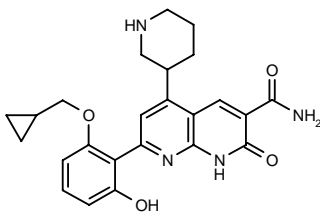


C18 H19 N3 O3; Mol wt: 325.3661

ACTION – An inhibitor of IκB kinase β (IKK-β) that is thus able to prevent the activation of NF-κB. Potentially useful for the treatment of asthma and other inflammatory conditions including allergic rhinitis, atopic dermatitis, conjunctivitis, chronic arthrorheumatism, systemic lupus erythematosus, psoriasis, sepsis, etc. Other exemplified 2-arylpyridine derivatives include the following:



Compound	R1	R2	R3	R4	A	Formula
319487	H	3-Pip	-O-		-CH ₂ -	C ₁₉ H ₂₁ N ₃ O ₂
319488	OPr	3-Pip	-O-		-CH ₂ -	C ₂₂ H ₂₇ N ₃ O ₃
319489	cyclopropyl-CH ₂ O	4-Pip	-O-		-O-	C ₂₂ H ₂₅ N ₃ O ₄
319490	cyclopropyl-CH ₂ O	3-Pip	H	H	-O-	C ₂₂ H ₂₇ N ₃ O ₃
319492	cyclopropyl-CH ₂ O	3-Pip	-O-		-CH(CONH ₂)-	C ₂₄ H ₂₈ N ₄ O ₄
319493	cyclopropyl-CH ₂ O	3-Pip	-O-		-N(CONH ₂)-	C ₂₃ H ₂₇ N ₅ O ₄
319494	cyclopropyl-CH ₂ O	3-Pip	-O-		-N(CONH ₂)-	C ₂₅ H ₃₁ N ₅ O ₄



319491: C24 H26 N4 O4

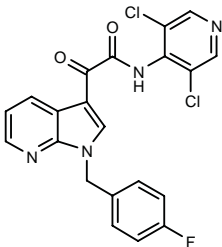
SOURCE – Bayer.

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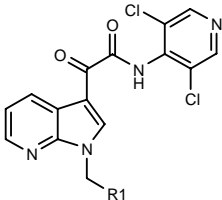
319539

N-(3,5-Dichloropyridin-4-yl)-2-[1-(4-fluorobenzyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-2-oxoacetamide



C21 H13 Cl2 F N4 O2; Mol wt: 443.2637

ACTION – Phosphodiesterase type 4 (PDE4) inhibitor (IC₅₀ = 0.004 μM) also shown to inhibit TNF-α release in nasal polyp cells by 92% at 0.3 μM. When administered to ovalbumin-sensitized rats, compound was able to prevent eosinophilia by 62% at 10 mg/kg i.p. and by 59% at 10 mg/kg p.o. Potentially useful for the treatment of a broad range of TNF-α-mediated disorders including asthma, arthritis, osteoporosis, sepsis, chronic pulmonary diseases, bone resorption disorders, transplant rejection, autoimmune diseases, lupus erythematosus, multiple sclerosis, glomerulonephritis, type 1 diabetes, viral and protozoal infections, AIDS, cachexia, allergic rhinitis, atopic dermatitis, Alzheimer’s disease, Parkinson’s disease, depression, stroke, benign prostatic hyperplasia, urinary incontinence, sexual dysfunction, etc. Other exemplified 7-azaindoles are:



Compound	R1	Formula
319540	4-Cl-Ph	C ₂₁ H ₁₃ Cl ₃ N ₄ O ₂
319541	4-MeO-Ph	C ₂₂ H ₁₆ Cl ₂ N ₄ O ₃
319542	i-Pr	C ₁₈ H ₁₆ Cl ₂ N ₄ O ₂

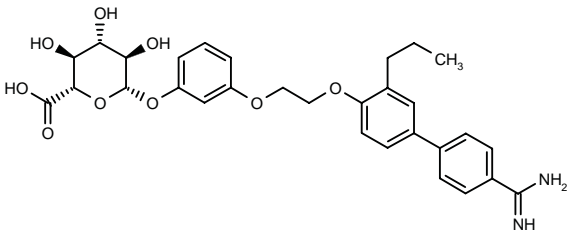
SOURCE – AWD.pharma.

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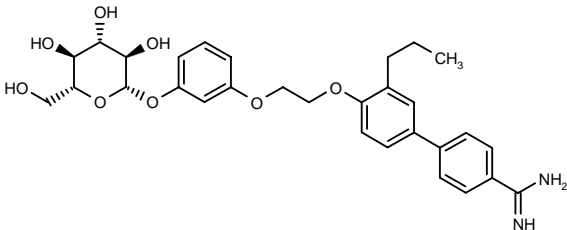
319554

1-*O*-[3-[2-(4'-Amidino-3-propylbiphenyl-4-yloxy)ethoxy]-phenyl]-β-D-glucopyranosiduronic acid



C30 H34 N2 O9; Mol wt: 566.6036

ACTION – Leukotriene B₄ (LTB₄) antagonist (K_i = 3.6 nM), potentially useful for the treatment of asthma, arthritis, chronic obstructive pulmonary disease, psoriasis, ulcerative colitis, cystic and pulmonary fibrosis, Alzheimer’s disease, ischemia and reperfusion injury, atherosclerosis, multiple sclerosis, autoimmune diseases, cancer and alveolitis. Another specifically claimed pyranoside derivative is:



319555: C30 H36 N2 O8

SOURCE – Boehringer Ingelheim.

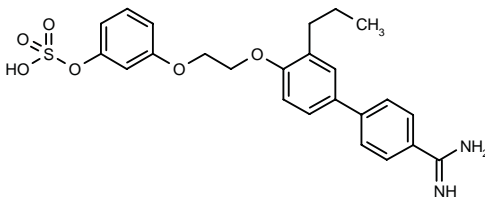
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319556

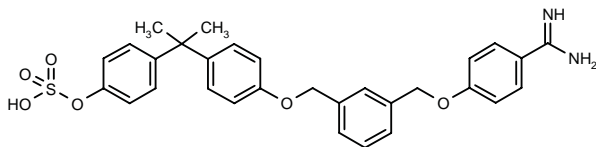
Sulfuric acid 3-[2-(4'-amidino-3-propylbiphenyl-4-yloxy)ethoxy]phenyl monoester

3'-Propyl-4'-[2-(3-sulfooxyphenoxy)ethoxy]biphenyl-4-carboxamidine



C24 H26 N2 O6 S; Mol wt: 470.5434

ACTION – Leukotriene B₄ (LTB₄) antagonist (K_i = 3.2 nM), potentially useful for the treatment of asthma, arthritis, chronic obstructive pulmonary disease, psoriasis, ulcerative colitis, cystic and pulmonary fibrosis, Alzheimer's disease, ischemia and reperfusion injury, atherosclerosis, multiple sclerosis, autoimmune diseases, cancer and alveolitis. Another exemplified benzamidine derivative is:



319557: C30 H30 N2 O6 S

SOURCE – Boehringer Ingelheim.

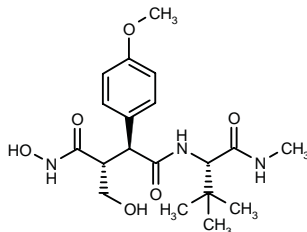
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PKF-242-484

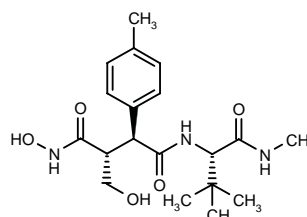
319688

*N*¹-[2,2-Dimethyl-1(*S*)-(N-methylcarbamoyl)propyl]-*N*⁴-hydroxy-3(*R*)-(hydroxymethyl)-2(*S*)-(4-methoxyphenyl)-succinamide



C19 H29 N3 O6; Mol wt: 395.4531

ACTION – Dual inhibitor of matrix metalloproteinases (MMP) and TNF-α-converting enzyme (TACE), giving K_i values of 0.1-4.5 nM against MMP-1 (collagenase 1), MMP-2 (gelatinase A), MMP-3 (stromelysin), MMP-9 (gelatinase B) and MMP-13 (collagenase 3), and of 0.6 nM for TACE. Compound inhibited TNF-α production in human peripheral blood mononuclear cells (PBMCs; IC₅₀ = 56.3 nM) but no significant effect was seen on other parameters of human peripheral blood leukocyte activation. *In vivo*, it inhibited lipopolysaccharide (LPS)-stimulated TNF-α release in rats (ED₅₀ = 1 mg/kg p.o.), as well as LPS-induced neutrophil and lymphocyte accumulation and TNF-α release in the bronchoalveolar lavage fluid (BALF) of mice following intranasal (3-30 mg/kg) or oral (10 mg/kg) administration. In a model of antigen-induced lung inflammation, compound significantly suppressed neutrophil, eosinophil and lymphocyte infiltration into BALF when given intranasally (1-10 mg/kg) before and after ovalbumin challenge. Potentially useful for the treatment of inflammatory lung diseases such as asthma and chronic obstructive pulmonary disease. Another related compound is:



PKF-241-466 [320383]: C19 H29 N3 O5

SOURCE – Novartis.

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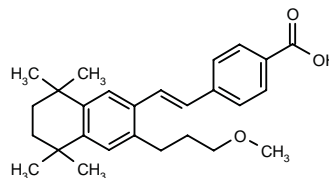
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3. Trifileff, A. et al. *Pharmacological profile of PKF242-484 and PKF241-466, novel dual inhibitors of TNF-α converting enzyme and matrix metalloproteinases, in models of airway inflammation*. Br J Pharmacol 2002, 135(7): 1655.

TREATMENT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASES

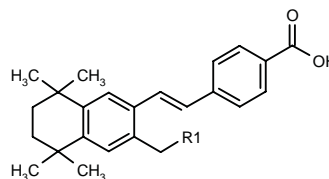
319657

4-[(*E*)-2-[3-(3-Methoxypropyl)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl]vinyl]benzoic acid



C27 H34 O3; Mol wt: 406.5626

ACTION – Retinoid receptor agonist with IC₅₀ values of 1800, 1400 and 210 nM, respectively, against retinoic acid receptors RARα, RARβ and RARγ in binding assays. Potentially useful for the treatment of chronic obstructive pulmonary disease and emphysema, as well as cancer and dermatological disorders. Other exemplified compounds are:



Compound	R1	Formula
319658	OMe	C ₂₅ H ₃₀ O ₃
319659	SBu	C ₂₈ H ₃₆ O ₂ S
319660	SCH ₂ CH(Me)Et	C ₂₉ H ₃₈ O ₂ S
319661	1-pyrrolyl	C ₂₈ H ₃₁ NO ₂
319664	2-furyl-CH ₂ S	C ₂₉ H ₃₂ O ₃ S
319665	OH	C ₂₄ H ₂₈ O ₃
319666	4-Me-1-pyrazolyl	C ₂₈ H ₃₂ N ₂ O ₂
319667	1-Me-5-tetrazolyl-S	C ₂₆ H ₃₀ N ₄ O ₂ S

SOURCE – Roche.

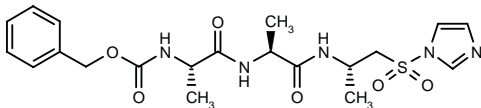
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1. Lapiere, J.-M. et al. (F. Hoffmann-La Roche AG) *New retinoids for the treatment of emphysema*. WO 0228810.

AGENTS FOR RESPIRATORY DISTRESS SYNDROME

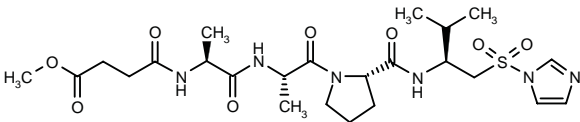
318769

N-(Benzyloxycarbonyl)-L-alanyl-L-alanine 2-(1*H*-imidazol-1-ylsulfonyl)-1(*S*)-methylethylamide



C20 H27 N5 O6 S; Mol wt: 465.5283

ACTION – An inhibitor of serine proteases with *in vitro* activity against human leukocyte elastase. Potentially useful for the treatment of a broad range of disorders including but not limited to respiratory distress syndrome, septic shock, multiple organ failure, emphysema, myocardial ischemia–reperfusion injury, dermatitis, cystic fibrosis, chronic bronchitis, atherosclerosis, Alzheimer’s disease, corneal ulcers, rheumatoid arthritis, acute pancreatitis, etc. Another exemplified imidazolylsulfonyl derivative is:



318771: C24 H38 N6 O8 S

SOURCE – Enzyme System Products.

REFERENCES

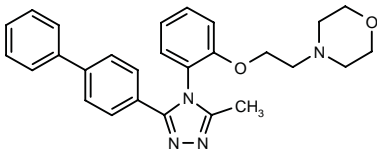
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CARDIOVASCULAR DRUGS

ANTIHYPERTENSIVE DRUGS

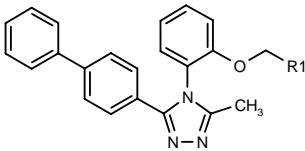
319344

4-[2-[2-[3-(Biphenyl-4-yl)-5-methyl-4*H*-1,2,4-triazol-4-yl]phenoxy]ethyl]morpholine



C27 H28 N4 O2; Mol wt: 440.5442

ACTION – Potent and selective antagonist of human vasopressin V_{1a} receptors, giving an IC₅₀ of 0.0221 μM for inhibition of vasopressin-induced Ca²⁺ accumulation in CHO cells expressing human V_{1a} receptors and exhibiting nanomolar affinity for human V_{1a} receptors (K_i = 34.8 nM), as well as 87-fold selectivity over human V₂ receptors. Potentially useful for the treatment of hypertension. Other related compounds are:



Compound	R1	Formula
319343	H	C ₂₂ H ₁₉ N ₃ O
320210	4-Me-1-Piz-CO	C ₂₈ H ₂₉ N ₅ O ₂

SOURCE – Yamanouchi.

REFERENCES

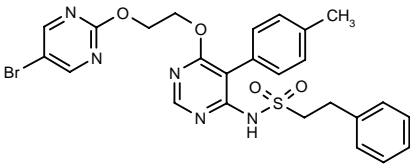
1. Suzuki, K. et al. (Yamanouchi Pharmaceutical Co., Ltd.) *Novel triazole derivs*. JP 2000063363.

2. Suzuki, T. et al. (Yamanouchi Pharmaceutical Co., Ltd.) *Novel triazole derivs*. WO 0158880.

3. Kakefuda, A. et al. *Discovery of 4,5-diphenyl-1,2,4-triazole derivatives as a novel class of selective antagonists for the human V_{1A} receptor*. Bioorg Med Chem 2002, 10(6): 1905.

319460

N-[6-[2-(5-Bromopyrimidin-2-yloxy)ethoxy]-5-(4-methylphenyl)pyrimidin-4-yl]-2-phenylethanesulfonamide



C25 H24 Br N5 O4 S; Mol wt: 570.4656

ACTION – Endothelin receptor antagonist with IC₅₀ values of 4 and 3310 nM, respectively, against ET_A and ET_B receptors expressed in CHO cells. In functional assays, compound inhibited endothelin-induced contractions in isolated rat aortic rings (mediated by ET_A receptors, pA₂ = 8.83) and tracheal rings (mediated by ET_B receptors, pA₂ = 7.07). Potentially useful for the treatment of vascular disorders such as hypertension, ischemia, vasospasm and angina pectoris, as well as other conditions including cancer, migraine, asthma and inflammation. Other exemplified arylalkane sulfonamides are:

SOURCE – Roche.

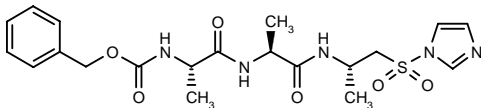
REFERENCES

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AGENTS FOR RESPIRATORY DISTRESS SYNDROME

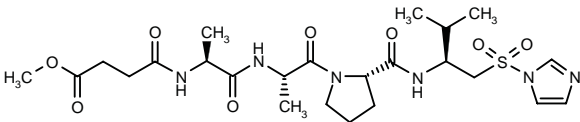
318769

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C20 H27 N5 O6 S; Mol wt: 465.5283

ACTION – An inhibitor of serine proteases with *in vitro* activity against human leukocyte elastase. Potentially useful for the treatment of a broad range of disorders including but not limited to respiratory distress syndrome, septic shock, multiple organ failure, emphysema, myocardial ischemia–reperfusion injury, dermatitis, cystic fibrosis, chronic bronchitis, atherosclerosis, Alzheimer’s disease, corneal ulcers, rheumatoid arthritis, acute pancreatitis, etc. Another exemplified imidazolylsulfonyl derivative is:



318771: C24 H38 N6 O8 S

SOURCE – Enzyme System Products.

REFERENCES

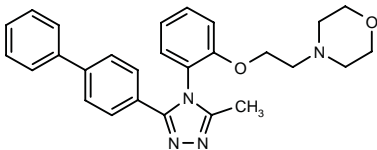
1. Rasnick, D.W. (Enzyme System Products) *Peptidyl sulfonyl imidazolides as selective inhibitors of serine proteases*. US 6358928.

CARDIOVASCULAR DRUGS

ANTIHYPERTENSIVE DRUGS

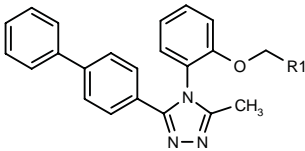
319344

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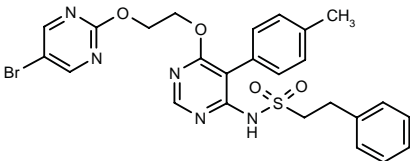
SOURCE – Yamanouchi.

REFERENCES

1. Suzuki, K. et al. (Yamanouchi Pharmaceutical Co., Ltd.) *Novel triazole derivs*. JP 2000063363.
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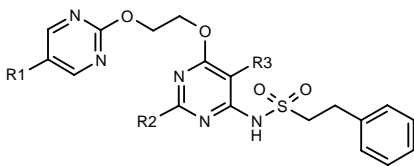
319460

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C25 H24 Br N5 O4 S; Mol wt: 570.4656

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Compound	R1	R2	R3	Formula
319463	Cl	2-pyrimidinyl	4-Me-Ph	C ₂₉ H ₂₆ ClN ₇ O ₄ S
319464	Br	2-pyrimidinyl	4-Me-Ph	C ₂₉ H ₂₆ BrN ₇ O ₄ S
319465	Br	H	3-MeO-PhO	C ₂₈ H ₂₄ BrN ₅ O ₆ S

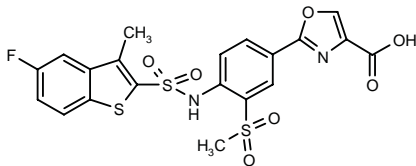
SOURCE – Actelion.

REFERENCES

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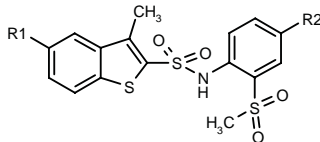
320020

2-[4-(5-Fluoro-3-methyl-1-benzothien-2-ylsulfonamido)-3-(methylsulfonyl)phenyl]oxazole-4-carboxylic acid



C20 H15 F N2 O7 S3; Mol wt: 510.5415

ACTION – Agent for the treatment of disorders caused by hyperproduction of angiotensin II or endothelin-1 that acts by inhibiting chymase (IC₅₀ = 2 nM), while exhibiting > 5,000-fold selectivity over chymotrypsin and cathepsin G. Compound was also shown to be stable in rat plasma. Potentially useful for the treatment of hypertension, cardiac hypertrophy, heart failure, myocardial infarction, arteriosclerosis, nephropathy, diabetic retinopathy, ischemia–reperfusion injury, postangioplasty restenosis, rheumatoid arthritis, psoriasis, allergy, inflammation, asthma, atopic dermatitis and cancer. Other exemplified *N*-phenyl-1-benzothien-2-sulfonamide derivatives include the following:



Compound	R1	R2	Formula
320021	Cl	CO ₂ Me	C ₁₈ H ₁₆ ClNO ₆ S ₃
320022	F	CO ₂ Me	C ₁₈ H ₁₆ FNO ₆ S ₃
320023	Cl	4-CO ₂ H-2-oxazolyl	C ₂₀ H ₁₅ ClN ₂ O ₇ S ₃

SOURCE – Toa Eiyo.

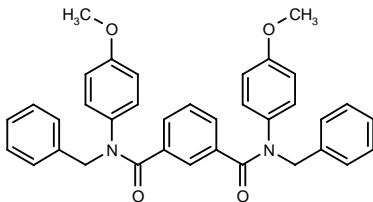
REFERENCES

1. Satoh, S. et al. (Toa Eiyo Ltd.) *N-Substd. benzothiophenesulfonamide derivs*. WO 0222595.

TREATMENT OF DISORDERS OF THE CORONARY ARTERIES AND ATHEROSCLEROSIS

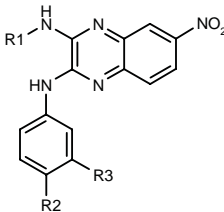
318941

N,N'-Dibenzyl-*N,N'*-bis(4-methoxyphenyl)isophthalamide

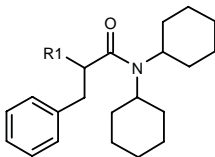


C36 H32 N2 O4; Mol wt: 556.6588

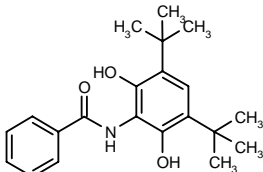
ACTION – Agent with the ability to modulate farnesoid X receptors, potentially useful for the treatment of atherosclerosis, peripheral vascular disease, cardiovascular disease, hypercholesterolemia, obesity, diabetes and inflammatory conditions associated with high or low cholesterol levels. Other exemplified compounds are:



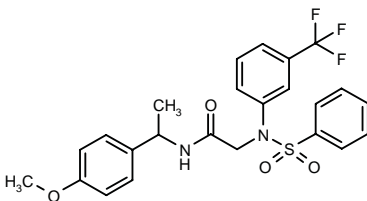
Compound	R1	R2	R3	Formula
318942	3,4-(Cl)2-Ph	Cl	Cl	C ₂₀ H ₁₁ Cl ₄ N ₅ O ₂
318944	cyclohexyl	Me	Me	C ₂₂ H ₂₈ N ₅ O ₂



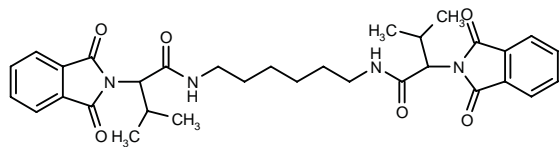
Compound	R1	Formula
318948	1,3-dioxo-2-isoindoliny	C ₂₉ H ₃₄ N ₂ O ₃
318950	N(Me)COPh	C ₂₉ H ₃₈ N ₂ O ₂



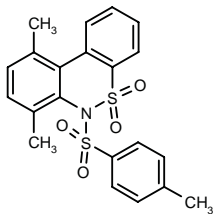
318945: C21 H27 N O3



318947: C24 H23 F3 N2 O4 S



318951: C32 H38 N4 O6



318952: C21 H19 N O4 S2

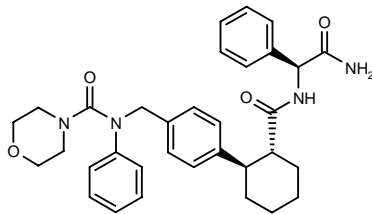
SOURCE – Tularik.

REFERENCES

1. Houze, J. et al. (Tularik Inc.) *FXR modulators*. WO 0220463.

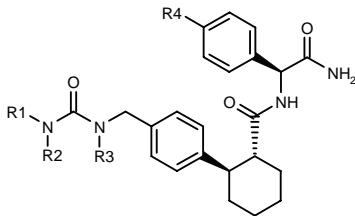
319045

N-[4-[2(*R*)-[*N*-[1(*S*)-Carbamoyl-1-phenylmethyl]-carbamoyl]-1(*R*)-cyclohexyl]benzyl]-*N*-phenylmorpholine-4-carboxamide



C33 H38 N4 O4; Mol wt: 554.6872

ACTION – Adenosine uptake inhibitor (IC₅₀ = 30 nM), potentially useful for the treatment of cardiovascular ischemic disorders including angina pectoris, peripheral and arterial occlusion, thrombotic disorders, myocardial infarction and reperfusion injury. Other exemplified compounds are:



Compound	R1	R2	R3	R4	Formula
319046	Me	Me	Ph	H	C ₃₁ H ₃₆ N ₄ O ₃
319047	Me	Me	cyclopropyl	H	C ₂₈ H ₃₆ N ₄ O ₃
319048	Et	Et	2-Pyr	H	C ₃₂ H ₃₉ N ₅ O ₃
319049	CH ₂ CH ₂ OH	Et	4-F-Ph	F	C ₃₃ H ₃₈ F ₂ N ₄ O ₄
319050	CH ₂ CH ₂ OH	Et	Ph	H	C ₃₃ H ₄₀ N ₄ O ₄

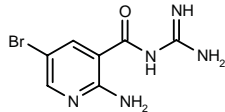
SOURCE – Bayer.

REFERENCES

1. Bischoff, E. et al. (Bayer AG) *Substd. phenylcyclohexane carboxylic acid amides and the use thereof*. DE 10044792, WO 0220472.

319290

N-(2-Amino-5-bromopyridin-3-ylcarbonyl)guanidine



C7 H8 Br N5 O; Mol wt: 258.0782

ACTION – Human platelet Na⁺/H⁺ exchange inhibitor, an amiloride derivative with improved inhibitory activity against acid-induced platelet swelling and ²²Na⁺ uptake (IC₅₀ = 0.85 and 0.8 μM, respectively). Potentially useful for the treatment of cardiac ischemia–reperfusion injury.

SOURCES – University of Liège, Liège (BE); University of Namur, Namur (BE); Therabel.

REFERENCES

1. Laeckmann, D. et al. *Synthesis and biological evaluation of aroylguanidines related to amiloride as inhibitors of the human platelet Na⁺/H⁺ exchanger*. Bioorg Med Chem 2002, 10(6): 1793.

Ptu1

318847

L-Alanyl-L-glutamyl-L-lysyl-L-aspartyl-L-cysteinyl-L-isoleucyl-L-alanyl-L-prolyl-glycyl-L-alanyl-L-prolyl-L-cysteinyl-L-phenylalanyl-glycyl-L-threonyl-L-aspartyl-L-lysyl-L-prolyl-L-cysteinyl-L-cysteinyl-L-asparaginyl-L-prolyl-L-arginyl-L-alanyl-L-tryptophyl-L-cysteinyl-L-seryl-L-seryl-L-tyrosyl-L-alanyl-L-asparaginyl-L-lysyl-L-cysteinyl-L-leucine

C153 H235 N43 O47 S6; Mol wt: 3621.1890

ACTION – Peptide isolated from venomous saliva of the assassin bugs *Peirates turpis*, *Agriosphodrus dohrni* and *Isyndus obscurus* that acts as an N-type calcium channel blocker. Ptu1 was shown to reversibly block N-type calcium channels expressed in BHK-6 cells with an IC₅₀ of 300 nM. This peptide is expected to be useful for the treatment of angina pectoris, hypertension, cardiomyopathy, arrhythmia and cerebral ischemia.

SOURCE – Suntory.

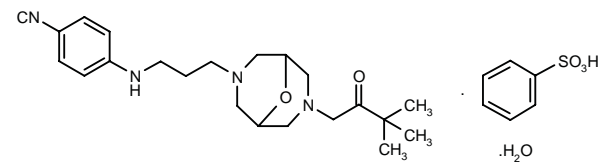
REFERENCES

1. Nakajima, K. et al. (Suntory Ltd.) *Novel peptide having calcium channel inhibitory effect*. JP 2002080499.

ANTIARRHYTHMIC DRUGS

319967

4-[3-[7-(3,3-Dimethyl-2-oxobutyl)-9-oxa-3,7-diazabicyclo-[3.3.1]non-3-yl]propylamino]benzonitrile benzenesulfonate hydrate



C22 H32 N4 O2 . C6 H6 O3 S . H2O; Mol wt: 560.7120

ACTION – Oxabispidine derivative, potentially useful for the treatment of atrial and ventricular arrhythmias.

SOURCE – AstraZeneca.

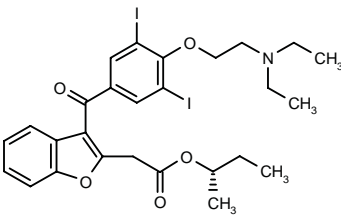
REFERENCES

1. Björnsne, M. et al. (AstraZeneca AB) *New oxabispidine cpd. useful in the treatment of cardiac arrhythmias.* WO 0228863.

(S)-ATI-2042

318814

2-[3-[4-[2-(Diethylamino)ethoxy]-3,5-diiodobenzoyl]-1-benzofuran-2-yl]acetic acid 1(S)-methylpropyl ester



C27 H31 I2 N O5; Mol wt: 703.3439

ACTION – Antiarrhythmic agent with a superior ability to inhibit ventricular premature beats and longer lasting effects following i.v. administration to rats as compared to the racemate. The plasma half-life of this compound was 7.3 h.

SOURCE – ARYx Therapeutics.

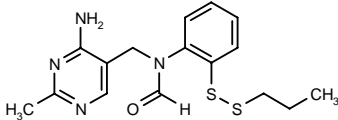
REFERENCES

1. Druzgala, P. and Milner, P.G. (ARYx Therapeutics, Inc.) *Enantiomeric cpds. for treatment of cardiac arrhythmias and methods of use.* US 6362223.

HEART FAILURE THERAPY

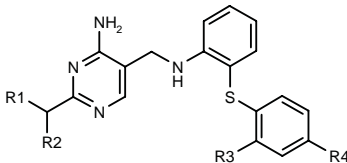
318752

N-(4-Amino-2-methylpyrimidin-5-ylmethyl)-N-[2-(propyldisulfanyl)phenyl]formamide

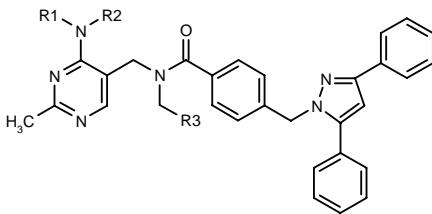


C16 H20 N4 O S2; Mol wt: 348.4930

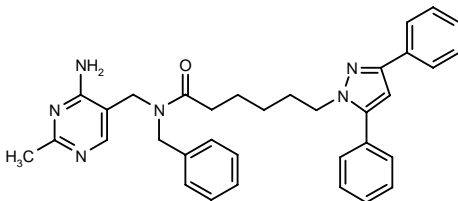
ACTION – G-protein-coupled receptor kinase (GRK), particularly GRK2, inhibitor, as demonstrated by its ability to inhibit GRK2-mediated phosphorylation of rhodopsin *in vitro* by more than 30% at 30 μM. Potentially useful for the treatment of heart failure, as well as other disorders mediated by β-adrenoceptors and other G-protein-coupled receptors such as hypertension, arteriosclerosis, bronchial asthma, drug abuse, Parkinson’s disease, dementia, peripheral arterial obstruction, diabetic nephropathy, urinary incontinence, depression and obesity. Other exemplified compounds are:



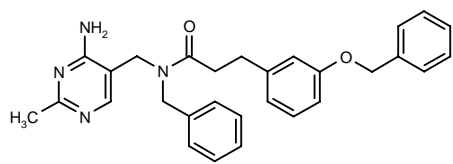
Compound	R1=R2	R3	R4	Formula
318754	H	H	OMe	C ₁₉ H ₂₀ N ₄ OS
318755	H	NO2	H	C ₁₈ H ₁₇ N ₅ O ₂ S
318759	Me	H	OMe	C ₂₁ H ₂₄ N ₄ OS



Compound	R1=R2	R3	Formula
318758	H	Ph	C ₃₆ H ₃₂ N ₆ O
318764	H	CH2CH2Ph	C ₃₈ H ₃₆ N ₆ O
318766	Me	Ph	C ₃₈ H ₃₆ N ₆ O



318760: C34 H36 N6 O



318762: C29 H30 N4 O2

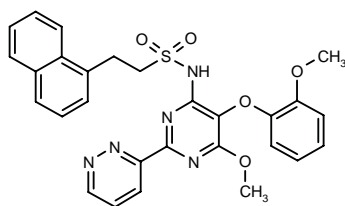
SOURCE – Takeda.

REFERENCES

1. Fukumoto, S. et al. (Takeda Chemical Industries, Ltd.) *GRK inhibitor*. WO 0218350.

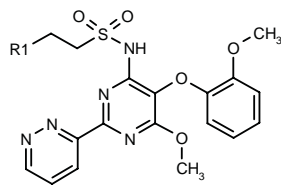
319596

N-[6-Methoxy-5-(2-methoxyphenoxy)-2-(3-pyridazinyl)-pyrimidin-4-yl]-2-(1-naphthyl)ethanesulfonamide



C28 H25 N5 O5 S; Mol wt: 543.6015

ACTION – Endothelin ET_A receptor antagonist, potentially useful for the treatment of congestive heart failure, restenosis, renal failure and systemic and pulmonary hypertension, among other endothelin-mediated disorders. Other specifically claimed pyridazine derivatives are:



Compound	R1	Formula
319597	4-F-Ph	C ₂₄ H ₂₂ FN ₅ O ₅ S
319598	cyclopentyl	C ₂₃ H ₂₇ N ₅ O ₅ S
319599	4-CO ₂ H-Ph	C ₂₈ H ₂₃ N ₅ O ₇ S
319600	Ph	C ₂₄ H ₂₃ N ₅ O ₅ S

SOURCE – Pfizer.

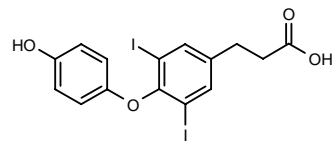
REFERENCES

1. Banks, B.J. et al. (Pfizer Inc.;Pfizer Ltd.) *New pyridazine endothelin antagonists*. EP 1191026, US 2002061889.

DITPA

296971

3-[4-(4-Hydroxyphenoxy)-3,5-diiodophenyl]propionic acid



C15 H12 I2 O4; Mol wt: 510.0558

ACTION – Thyroid hormone analogue with low metabolic activity, able to exert positive inotropic effects and to improve left ventricular performance. Results from a pilot clinical trial in patients with congestive heart failure showed that compound improved diastolic function, increased cardiac index and lowered peripheral vascular resistance; serum cholesterol and triglycerides were also reduced. Potentially useful for the treatment of congestive heart failure.

SOURCES – University of Arizona, Tucson, AZ (US); University of Utah, Salt Lake City, UT (US).

REFERENCES

1. Halow, J.M. et al. *Treatment with a thyroid hormone analogue improves LV function in heart failure induced by pressure-overload*. Circulation 1996, 94(8): Abst 0381.

2. Litwin, S.E. et al. *DITPA prevents the blunted contraction-frequency relationship in myocytes from infarcted hearts*. Am J Physiol 2000, 278(3, Part 2): H862.

3. Morkin, E. et al. *Pilot studies on the use of 3,5-diiodothyropropionic acid in heart failure*. J Am Coll Cardiol 2002, 39(9, Suppl. B): 405B.

4. Morkin, E. Jr. et al. *Preliminary studies on the use of 3,5-diiodothyropropionic acid, a thyroid hormone analog, in the treatment of congestive heart failure*. J Am Coll Cardiol 2001, 37(2, Suppl. A): 172A.

5. Pennock, G. et al. *Comparison of the cardiac effects of thyroxine and 3,5-diiodothyropropionic acid, a thyroid analogue with inotropic selectivity*. Circulation 1991, 84(4, Suppl. 2): Abst 1600.

6. Pennock, G.D. et al. *Cardiac effects of 3,5-diiodothyropropionic acid, a thyroid hormone with inotropic selectivity*. J Pharmacol Exp Ther 1992, 263(1): 163.

7. Pennock, G.D. et al. *Combination treatment with captopril and the thyroid hormone analog 3,5-diiodothyropropionic acid. A new approach to improving left ventricular performance in heart failure*. Circulation 1993, 88(3): 1289.

8. Pennock, G.D. et al. *Identification of simple substituted phenols with thyromimetic activity: Cardiac effects of 3,5-diiodo-4-hydroxyphenylpropionic acid*. J Pharmacol Exp Ther 1993, 268(1): 216.

9. Pennock, G.D. et al. *Intracellular Ca²⁺ uptake and release in postinfarction heart failure: Enhancement with an analogue of thyroid hormone*. Circulation 1994, 90(4, Part 2): Abst 1417.

10. Pennock, G.D. et al. *Prevention of abnormal sarcoplasmic reticulum calcium transport and protein expression in post-infarction heart failure using 3,5-diiodothyropropionic acid (DITPA)*. J Mol Cell Cardiol 2000, 32(11): 1939.

11. Sponner, P.H. et al. *Impaired large artery vasorelaxation is restored with the thyroid hormone analogue 3,5-diiodothyropropionic acid (DITPA)*. J Invest Med 2001, 49(1): Abst 361.

12. Wickenden, A.D. et al. *Chronic treatment with the thyroid hormone analog, DITPA, restores K⁺ channel expression and repolarization in hypertrophied rat ventricular myocytes*. Circulation 1998, 98(17): Abst 1808.

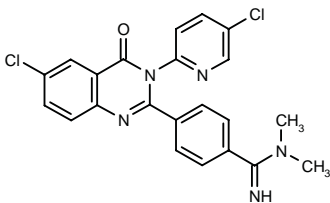
13. Wickenden, A.D. et al. *The thyroid hormone analog DITPA restores I_{to} in rats after myocardial*. Am J Physiol 2000, 278(4, Part 2): H1105.

AGENTS AFFECTING BLOOD COAGULATION

ANTICOAGULANTS

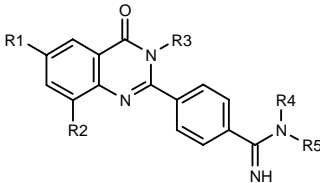
318607

4-[6-Chloro-3-(5-chloropyridin-2-yl)-4-oxo-3,4-dihydro-quinazolin-2-yl]-*N,N*-dimethylbenzamidine

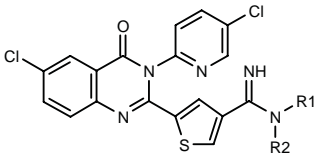


C22 H17 Cl2 N5 O; Mol wt: 438.3163

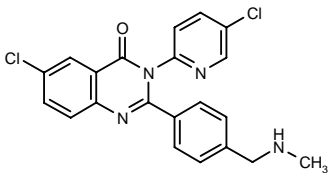
ACTION – Factor Xa inhibitor, potentially useful for the treatment of thrombotic disorders including acute coronary syndrome, myocardial infarction, angina, embolic stroke, thrombotic stroke, transient ischemic attacks, venous thrombosis, deep venous thrombosis, pulmonary embolism, coagulopathy, disseminated intravascular coagulation and thrombocytopenic purpura. Other exemplified quinazolin-4(3*H*)-one derivatives include the following:



Compound	R1	R2	R3	R4	R5	Formula
318609	OMe	H	5-Cl-2-Pyr	Me	Me	C ₂₃ H ₂₀ ClN ₅ O ₂
318612	Cl	Cl	5-Cl-2-Pyr	-(CH2)4-		C ₂₄ H ₁₆ Cl ₃ N ₅ O
318613	H	H	4-Cl-Ph	-(CH2)5-		C ₂₆ H ₂₃ ClN ₄ O
318615	H	H	4-F-Ph	Me	Me	C ₂₃ H ₁₉ FN ₄ O



Compound	R1	R2	Formula
318616	Me	Et	C ₂₁ H ₁₇ Cl ₂ N ₅ OS
318617	Me	CH2CH2OMe	C ₂₂ H ₁₉ Cl ₂ N ₅ O ₂ S
318618		-(CH2)4-	C ₂₂ H ₁₇ Cl ₂ N ₅ OS



318620: C21 H16 Cl2 N4 O

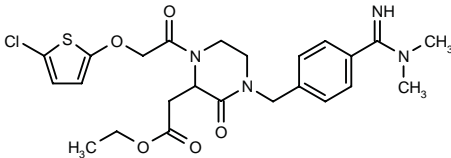
SOURCE – Millennium.

REFERENCES

1. Zhang, P. et al. (COR Therapeutics, Inc.) *Bicyclic pyrimidin-4-one based inhibitors of factor Xa*. WO 0226718.

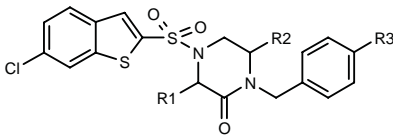
318625

2-[1-[2-(5-Chlorothiophen-2-yloxy)acetyl]-4-[4-(*N,N*-dimethylamidino)benzyl]-3-oxopiperazin-2-yl]acetic acid ethyl ester

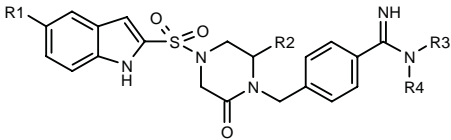


C24 H29 Cl N4 O5 S; Mol wt: 521.0351

ACTION – Factor Xa inhibitor, potentially useful for the treatment of thrombotic disorders including acute coronary syndrome, myocardial infarction, angina, embolic stroke, thrombotic stroke, transient ischemic attacks, venous thrombosis, deep venous thrombosis, pulmonary embolism, coagulopathy, disseminated intravascular coagulation and thrombocytopenic purpura. Other exemplified piperazin-2-one amides include the following:



Compound	R1	R2	R3	Formula
318626	CH2CO2H	H	1-Me-4,5-dihydro-2-imidazolyl	C ₂₅ H ₂₅ ClN ₄ O ₅ S ₂
318628	H	H	4-(CO2Et)-1-Pip-C(=NH)	C ₂₈ H ₃₁ ClN ₄ O ₅ S ₂
318631	H	CO2H	ethynyl-CH2N(Me)C(=NH)	C ₂₅ H ₂₃ ClN ₄ O ₅ S ₂
318632	H	CO2H	2-Pyr-CH2CH2N(Me)C(=NH)	C ₂₉ H ₂₈ ClN ₅ O ₅ S ₂



Compound	R1	R2	R3	R4	Formula
318629	Cl	H	Me	CH2CH2Ph	C ₂₉ H ₃₀ ClN ₅ O ₃ S
318630	Cl	H	Me	ethynyl-CH2	C ₂₄ H ₂₄ ClN ₅ O ₃ S
318633	Me	CO2H	-(CH2)5-		C ₂₇ H ₃₁ N ₅ O ₃ S
318634	Cl	CO2H	Me	CH2CHO	C ₂₄ H ₂₄ ClN ₅ O ₆ S

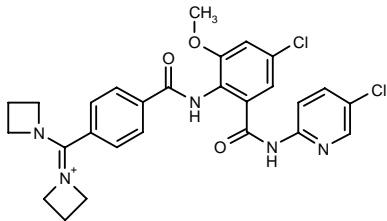
SOURCE – Millennium.

REFERENCES

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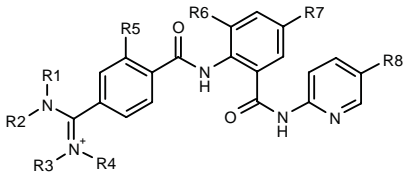
319175

1-[1-(1-Azetidinyl)-1-[4-[N-[4-chloro-2-[N-(5-chloropyridin-2-yl)carbamoyl]-6-methoxyphenyl]carbamoyl]phenyl]-methylene]azetidinium



C27 H26 Cl2 N5 O3; Mol wt: 539.4404

ACTION – An inhibitor of factor Xa, potentially useful for the treatment of thrombotic disorders including acute coronary syndrome, myocardial infarction, unstable and refractory angina, occlusive coronary thrombus following thrombolytic therapy or coronary angioplasty, embolic stroke, thrombotic stroke, venous thrombosis, deep venous thrombosis, pulmonary embolism, coagulopathy and disseminated intravascular coagulation, among others. Other exemplified compounds are:



Compound	R1	R2	R3	R4	R5	R6	R7	R8	Formula
319176	-(CH2)3-	-(CH2)3-			H	OH	H	Cl	C ₂₆ H ₂₅ ClN ₅ O ₃
319177	-(CH2)3-	-(CH2)3-			F	H	H	Br	C ₂₆ H ₂₄ BrFN ₅ O ₂
319178	-(CH2)3-	-(CH2)3-			H	H	F	Cl	C ₂₆ H ₂₄ ClFN ₅ O ₂
319179	-(CH2)3-	-(CH2)3-			H	N(Me)2	Cl	Cl	C ₂₆ H ₂₉ Cl ₂ N ₆ O ₂
319180	-(CH2)3-	-(CH2)3-			H	N(Me)CH2-CH2OMe	Cl	Cl	C ₃₀ H ₃₃ Cl ₂ N ₆ O ₃
319181	Me	-(CH2)3-		Me	F	OMe	Cl	Cl	C ₂₆ H ₂₅ Cl ₂ FN ₅ O ₃
319182	Me	-(CH2)2-		(CH2)3OH	H	H	Cl	Cl	C ₂₆ H ₂₆ Cl ₂ N ₅ O ₃
319183	Me	Me	Me	Me	F	OMe	Cl	Cl	C ₂₅ H ₂₅ Cl ₂ FN ₅ O ₃

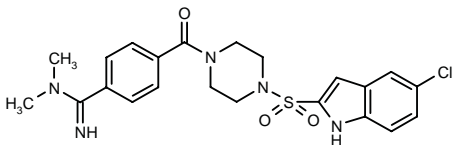
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REFERENCES

1. Zhu, B.-Y. et al. (COR Therapeutics, Inc.) *Quaternary amidino based inhibitors of factor Xa*. WO 0226731.

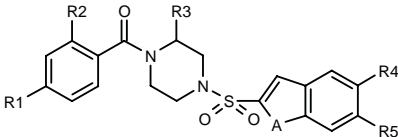
319184

4-[4-(5-Chloro-1*H*-indol-2-ylsulfonyl)piperazin-1-yl]-carbonyl]-*N,N*-dimethylbenzamide

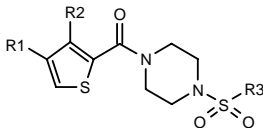


C22 H24 Cl N5 O3 S; Mol wt: 473.9826

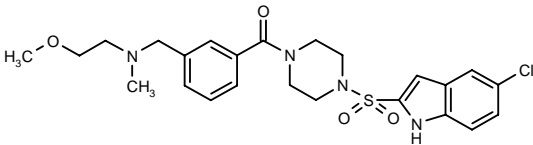
ACTION – An inhibitor of factor Xa, potentially useful for the treatment of thrombotic disorders including acute coronary syndrome, myocardial infarction, unstable and refractory angina, occlusive coronary thrombus following thrombolytic therapy or coronary angioplasty, embolic stroke, thrombotic stroke, venous thrombosis, deep venous thrombosis, pulmonary embolism, coagulopathy and disseminated intravascular coagulation, among others. Other exemplified piperazine-based compounds are:



Compound	R1	R2	R3	R4	R5	A	Formula
319186	1-azetidiny-C(=NH)	H	H	H	Cl	S	C ₂₃ H ₂₃ ClN ₄ O ₃ S ₂
319187	C(=NH)N(Me)Pr	F	H	Cl	H	NH	C ₂₄ H ₂₇ ClFN ₅ O ₃ S
319188	1,3-(Me)2-4,5-dihydroimidazolium-2-yl	OMe	H	Cl	H	NH	C ₂₅ H ₂₉ ClN ₆ O ₄ S
319194	C(=NH)N(Me)Et	H	CO2H	Cl	H	NH	C ₂₄ H ₂₆ ClN ₅ O ₃ S



Compound	R1	R2	R3	Formula
319190	C(=NH)NH2	H	6-Cl-2-benzothienyl	C ₁₈ H ₁₇ ClN ₄ O ₃ S ₃
319192	C(=NH)NHMe	Cl	6-Cl-2-benzothienyl	C ₁₉ H ₁₈ Cl ₂ N ₄ O ₃ S ₃
319196	3,4-dihydro-2H-pyrrol-5-yl-N(Me)CH2	Cl	6-Br-2-Naph	C ₂₅ H ₂₆ BrClN ₄ O ₃ S ₂



319195: C24 H29 Cl N4 O4 S

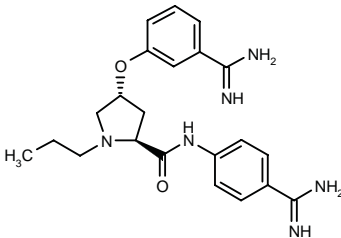
SOURCE – Millennium.

REFERENCES

1. Zhu, B.-Y. et al. (COR Therapeutics, Inc.) *Piperazine based inhibitors of factor Xa*. WO 0226720.

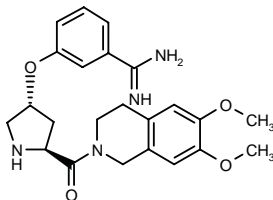
319274

4(*R*)-(3-Amidinophenoxy)-*N*-(4-amidinophenyl)-1-propyl-L-prolinamide



C22 H28 N6 O2; Mol wt: 408.5032

ACTION – An inhibitor of serine proteases with activity against factor VIIa ($K_i = 7.8 \mu\text{M}$), factor Xa ($K_i = 0.297 \mu\text{M}$), thrombin ($K_i = 4.744 \mu\text{M}$), trypsin ($K_i = 0.866 \mu\text{M}$), plasmin ($K_i = 7.36 \mu\text{M}$) and kallikrein ($K_i = 6.559 \mu\text{M}$). Potentially useful for the prevention of arterial and venous thrombosis. Another exemplified pyrrolidine-containing benzamidine derivative is:



319275: C23 H28 N4 O4

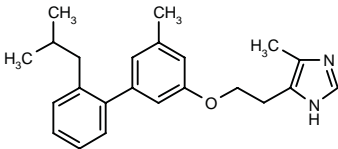
SOURCE – Genentech.

REFERENCES

1. Pastor, R.M. et al. (Genentech, Inc.) *Amidine inhibitors of serine proteases*. US 2002055469, WO 0222575.

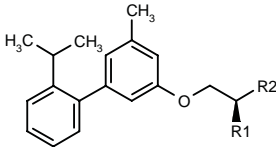
319288

5-[2-(2'-Isobutyl-5-methylbiphenyl-3-yloxy)ethyl]-4-methyl-1*H*-imidazole



C23 H28 N2 O; Mol wt: 348.4872

ACTION – Thrombin inhibitor with potential in the treatment of venous thromboembolism, pulmonary embolism, deep venous thrombosis and thromboembolic stroke, among other coagulation and cardiovascular disorders. Other exemplified compounds are:



Compound	R1	R2	Formula
319291	Me	4-Pyr-NH	C ₂₄ H ₂₈ N ₂ O
319293	H	2-(1-tetrazolyl)-Ph	C ₂₅ H ₂₆ N ₄ O
319296	H	4-Me-5-imidazolyl	C ₂₂ H ₂₆ N ₂ O

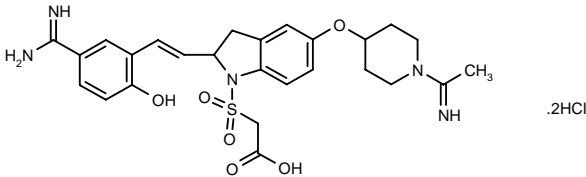
SOURCE – Merck & Co.

REFERENCES

1. Isaacs, R.C. et al. (Merck & Co., Inc.) *Thrombin inhibitors*. WO 0222584.

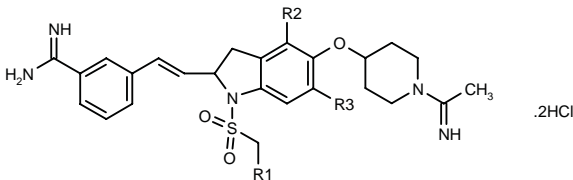
319472

2-[2-[(*E*)-2-(5-Amidino-2-hydroxyphenyl)vinyl]-5-[1-(1-iminoethyl)piperidin-4-yloxy]-2,3-dihydro-1*H*-indol-1-yl-sulfonyl]acetic acid dihydrochloride



C26 H31 N5 O6 S . 2HCl; Mol wt: 614.5477

ACTION – Anticoagulant with factor Xa-inhibitory activity ($\text{IC}_{50} = 4.4 \text{ nM}$) and potential in the treatment of coagulation disorders including cerebral infarction, myocardial infarction and peripheral circulatory disorders. Other exemplified styrene derivatives include the following:



Compound	R1	R2	R3	Isomer	Formula
319473	CO2H	H	H		C ₂₆ H ₃₁ N ₅ O ₆ S.2HCl
319474	Me	Cl	H		C ₂₆ H ₃₂ ClN ₅ O ₆ S.2HCl
319475	CO2Et	Cl	H		C ₂₈ H ₃₄ ClN ₅ O ₆ S.2HCl
319476	CO2Et	Me	H		C ₂₈ H ₃₇ N ₅ O ₆ S.2HCl
319477	CO2Et	CF3	H		C ₂₉ H ₃₄ F ₃ N ₅ O ₆ S.2HCl
319478	CO2Et	H	CF3		C ₂₉ H ₃₄ F ₃ N ₅ O ₆ S.2HCl
319479	CO2Et	H	CONH2		C ₂₉ H ₃₆ N ₆ O ₆ S.2HCl
319480	Me	H	H		C ₂₆ H ₃₃ N ₅ O ₆ S.2HCl
319481	CO2Et	H	H		C ₂₈ H ₃₅ N ₅ O ₆ S.2HCl
319482	CO2Et	Cl	H		C ₂₈ H ₃₄ ClN ₅ O ₆ S.2HCl
319483	CO2Et	H	Cl		C ₂₈ H ₃₄ ClN ₅ O ₆ S.2HCl
319484	CO2Et	H	H	R	C ₂₈ H ₃₄ ClN ₅ O ₆ S.2HCl
319485	CO2H	H	H	R	C ₂₆ H ₃₀ ClN ₅ O ₆ S.2HCl

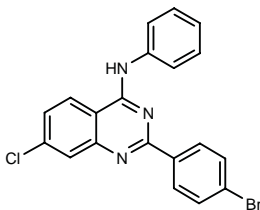
SOURCE – Sankyo.

REFERENCES

1. Fujimoto, K. et al. (Sankyo Co., Ltd.) *Styrene derivs*. JP 2002088080.

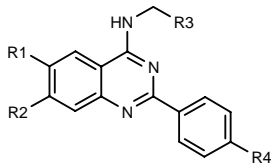
319505

2-(4-Bromophenyl)-7-chloro-*N*-phenylquinazolin-4-amine

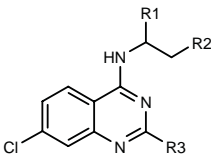


C20 H13 Br Cl N3; Mol wt: 410.7007

ACTION – Glycoprotein IbIX (gplbIX) receptor antagonist that is able to prevent its interaction with von Willebrand factor (vWF). Potentially useful for the treatment of thrombotic disorders including myocardial infarction, arteriosclerosis, angina pectoris, acute coronary syndromes, peripheral vascular disorders, stroke, transient ischemic attacks and postangioplasty reocclusion or restenosis. Other exemplified 4-aminoquinazolines include the following:



Compound	R1	R2	R3	R4	Formula
319506	H	Cl	Ph	Br	C ₂₁ H ₁₅ BrClN ₃
319507	Me	H	2-[2-(CH ₂ OH)-PhS]-Ph	Br	C ₂₉ H ₂₄ BrN ₃ OS
319508	OMe	OMe	2-oxo-1-pyrrolidinyl-CH ₂ CH ₂	Br	C ₂₃ H ₂₅ BrN ₄ O ₃
319509	H	Cl	1-Piz-CH ₂	Ph	C ₂₆ H ₂₆ ClN ₅



Compound	R1	R2	R3	Formula
319510	H	CH ₂ N(Et) ₂	4-(4-MeO-Ph)-Ph	C ₂₈ H ₃₁ ClN ₄ O
319512	H	1-Me-perhydro-3-indolyl	4-F-Ph-Ph	C ₃₁ H ₃₂ ClFN ₄
319514	H	1-Me-perhydro-3-indolyl	5-(4-F-Ph)-2-thienyl	C ₂₉ H ₃₀ ClFN ₄ S
319515	Me	CH ₂ CH ₂ N(Et) ₂	5-MeO-3-indolyl-NH	C ₂₆ H ₃₃ ClN ₆ O

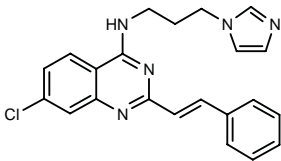
SOURCE – Merck KGaA.

REFERENCES

1. Mederski, W. et al. (Merck Patent GmbH) 4-Amino-quinazolines. WO 0224667.

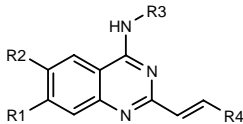
319516

7-Chloro-*N*-[3-(1*H*-imidazol-1-yl)propyl]-2-(2-phenylvinyl)-quinazolin-4-amine



C22 H20 Cl N5; Mol wt: 389.8880

ACTION – Glycoprotein IbIX (gplbIX) receptor antagonist that is able to prevent its interaction with von Willebrand factor (vWF). Potentially useful for the treatment of thrombotic disorders including myocardial infarction, arteriosclerosis, angina pectoris, acute coronary syndromes, peripheral vascular disorders, stroke, transient ischemic attacks and postangioplasty reocclusion or restenosis. Other exemplified 4-aminoquina-zolines include the following:



Compound	R1	R2	R3	R4	Formula
319517	Cl	H	CH ₂ CH ₂ N(Et) ₂	Ph	C ₂₂ H ₂₅ ClN ₄
319518	Cl	H	4-morpholinyl-(CH ₂) ₃	Ph	C ₂₃ H ₂₅ ClN ₄ O
319519	Cl	H	2-oxo-1-pyrrolidinyl-(CH ₂) ₃	Ph	C ₂₃ H ₂₃ ClN ₄ O
319520	Cl	H	4-NH ₂ -PhCH ₂ CH ₂	Ph	C ₂₄ H ₂₁ ClN ₄
319521	Cl	H	(CH ₂) ₃ N(Et) ₂	Ph	C ₂₃ H ₂₇ ClN ₄
319522	Cl	H	CH(Me)(CH ₂) ₃ N(Et) ₂	CH=CHPh	C ₂₇ H ₃₃ ClN ₄
319523	H	I	(CH ₂) ₃ N(Et) ₂	5-(2-thienyl)-2-thienyl	C ₂₅ H ₂₇ IN ₄ S ₂
319524	Cl	H	3-(NH ₂ CH ₂)-cyclohexyl-CH ₂	5-(2-thienyl)-2-thienyl	C ₂₆ H ₂₇ ClN ₄ S ₂

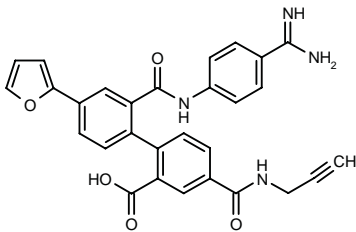
SOURCE – Merck KGaA.

REFERENCES

1. Mederski, W. et al. (Merck Patent GmbH) 4-Amino-quinazolines. WO 0224666.

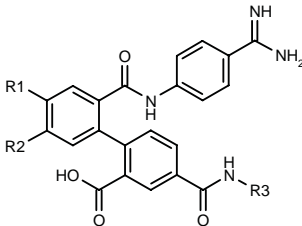
319558

2'-[*N*-(4-Amidinophenyl)carbamoyl]-4'-(2-furyl)-4-[*N*-(2-propynyl)carbamoyl]biphenyl-2-carboxylic acid



C29 H22 N4 O5; Mol wt: 506.5158

ACTION – An inhibitor of trypsin-like serine proteases such as tissue factor (TF)/factor VIIa, trypsin and thrombin, with respective IC₅₀ values of < 100 nM, > 100 nM and > 1 μM. Potentially useful for the treatment of thrombotic disorders including thrombolympangitis, thrombosinusitis, thromboendocarditis, thromboangiitis and thromboarteritis. Other exemplified biaryl compounds are:



Compound	R1	R2	R3	Formula
319559	4-Pyr	H	i-Bu	C ₃₁ H ₂₉ N ₅ O ₄
319560	5-(CH ₂ OH)-2-thienyl	H	i-Bu	C ₃₁ H ₃₀ N ₄ O ₅ S
319561	2-thiazolyl	H	i-Bu	C ₂₉ H ₂₇ N ₅ O ₄ S
319562	HOC(Me) ₂ -ethynyl	H	i-Bu	C ₃₁ H ₃₂ N ₄ O ₅
319563	H	OPh	i-Bu	C ₃₂ H ₃₀ N ₄ O ₅
319564	H	2-thienyl	i-Bu	C ₃₀ H ₂₈ N ₄ O ₄ S
319565	vinyl	H	CH(Pr) ₂	C ₃₁ H ₃₄ N ₄ O ₄
319566	2-furyl	H	(CH ₂) ₅ CO ₂ H	C ₃₂ H ₃₀ N ₄ O ₇
319567	vinyl	H	i-Bu	C ₂₈ H ₂₈ N ₄ O ₄

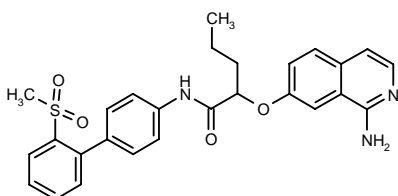
SOURCE – BioCryst.

REFERENCES

1. Babu, Y.S. et al. (BioCryst Pharmaceuticals, Inc.) *Biaryl cpds. as serine protease inhibitors*. WO 0234711.

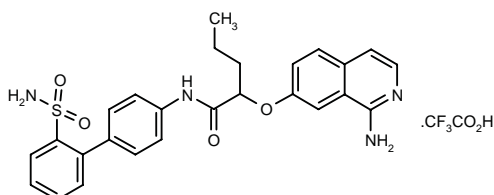
320061

2-(1-Aminoisoquinolin-7-yloxy)-N-[2'-(methylsulfonyl)-biphenyl-4-yl]pentanamide



C27 H27 N3 O4 S; Mol wt: 489.5933

ACTION – Anticoagulant, an inhibitor of factor Xa with potential utility in the treatment of thrombosis, myocardial infarction, arteriosclerosis, inflammation, stroke, angina pectoris, postangioplasty restenosis and intermittent claudication. Another exemplified amino heterocyclic compound is:



320063: C26 H26 N4 O4 S . C2 H F3 O2

SOURCE – Merck KGaA.

REFERENCES

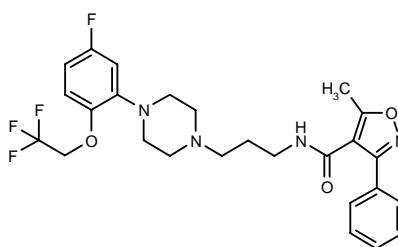
1. Dorsch, D. et al. (Merck Patent GmbH) *Amino heterocyclic cpds. (factor Xa inhibitors 14)*. DE 10046272, WO 0224654.

RENAL-UROLOGIC DRUGS

BENIGN PROSTATIC HYPERPLASIA THERAPY

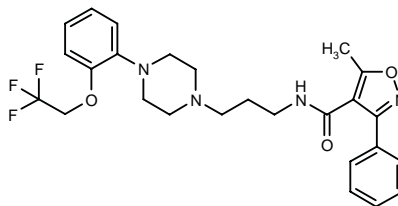
319140

N-[3-[4-[5-Fluoro-2-(2,2,2-trifluoroethoxy)phenyl]piperazin-1-yl]propyl]-5-methyl-3-phenylisoxazole-4-carboxamide



C26 H28 F4 N4 O3; Mol wt: 520.5242

ACTION – Agent with the ability to block α_1 -adrenoceptors while being selective over 5-HT_{1A} receptors and devoid of blood pressure-lowering activity. Compound gave K_i values of 0.05, 11.52, 0.33 and 191.74 nM, respectively, against α_{1A} -, α_{1B} - and α_{1D} -adrenoceptors and 5-HT_{1A} receptors in binding assays, and it demonstrated functional α_1 -antagonist activity *in vitro*. *In vivo*, it was able to reduce noradrenaline- and hypogastric nerve stimulation-induced urethral contractions in dogs with ID₅₀ values of 2.7 and 3.4 μ g/kg i.v., respectively. Potentially useful for the treatment of benign prostatic hyperplasia, excessive intraocular pressure, cardiac arrhythmia, erectile dysfunction and lower urinary tract dysfunction, as well as for inhibiting cholesterol biosynthesis and reducing sympathetically mediated pain. Another exemplified isoxazole-4-carboxamide compound is:



319141: C26 H29 F3 N4 O3

SOURCE – Recordati.

REFERENCES

1. Leonardi, A. et al. (Recordati Industria Chimica e Farmaceutica SpA) *Isoxazolecarboxamide derivs*. US 6365591.

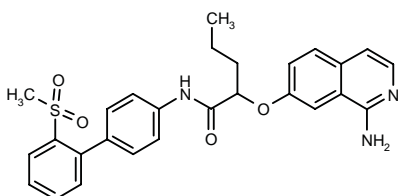
SOURCE – BioCryst.

REFERENCES

1. Babu, Y.S. et al. (BioCryst Pharmaceuticals, Inc.) *Biaryl cpds. as serine protease inhibitors*. WO 0234711.

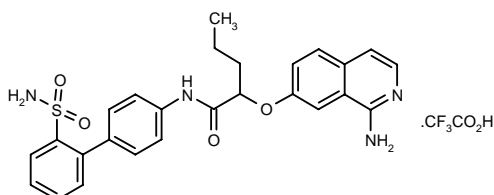
320061

2-(1-Aminoisoquinolin-7-yloxy)-N-[2'-(methylsulfonyl)-biphenyl-4-yl]pentanamide



C27 H27 N3 O4 S; Mol wt: 489.5933

ACTION – Anticoagulant, an inhibitor of factor Xa with potential utility in the treatment of thrombosis, myocardial infarction, arteriosclerosis, inflammation, stroke, angina pectoris, postangioplasty restenosis and intermittent claudication. Another exemplified amino heterocyclic compound is:



320063: C26 H26 N4 O4 S . C2 H F3 O2

SOURCE – Merck KGaA.

REFERENCES

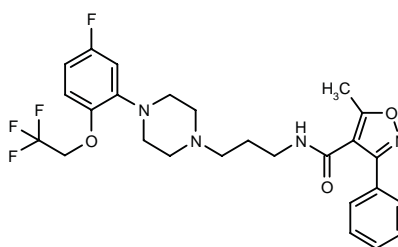
1. Dorsch, D. et al. (Merck Patent GmbH) *Amino heterocyclic cpds. (factor Xa inhibitors 14)*. DE 10046272, WO 0224654.

RENAL-UROLOGIC DRUGS

BENIGN PROSTATIC HYPERPLASIA THERAPY

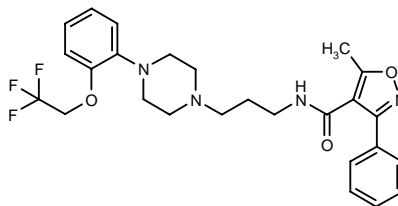
319140

N-[3-[4-[5-Fluoro-2-(2,2,2-trifluoroethoxy)phenyl]piperazin-1-yl]propyl]-5-methyl-3-phenylisoxazole-4-carboxamide



C26 H28 F4 N4 O3; Mol wt: 520.5242

ACTION – Agent with the ability to block α_1 -adrenoceptors while being selective over 5-HT_{1A} receptors and devoid of blood pressure-lowering activity. Compound gave K_i values of 0.05, 11.52, 0.33 and 191.74 nM, respectively, against α_{1A} -, α_{1B} - and α_{1D} -adrenoceptors and 5-HT_{1A} receptors in binding assays, and it demonstrated functional α_1 -antagonist activity *in vitro*. *In vivo*, it was able to reduce noradrenaline- and hypogastric nerve stimulation-induced urethral contractions in dogs with ID₅₀ values of 2.7 and 3.4 μ g/kg i.v., respectively. Potentially useful for the treatment of benign prostatic hyperplasia, excessive intraocular pressure, cardiac arrhythmia, erectile dysfunction and lower urinary tract dysfunction, as well as for inhibiting cholesterol biosynthesis and reducing sympathetically mediated pain. Another exemplified isoxazole-4-carboxamide compound is:



319141: C26 H29 F3 N4 O3

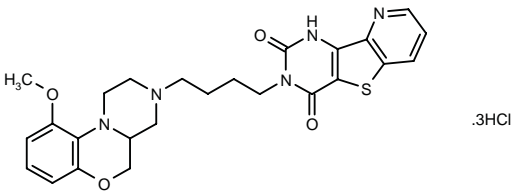
SOURCE – Recordati.

REFERENCES

1. Leonardi, A. et al. (Recordati Industria Chimica e Farmaceutica SpA) *Isoxazolecarboxamide derivs*. US 6365591.

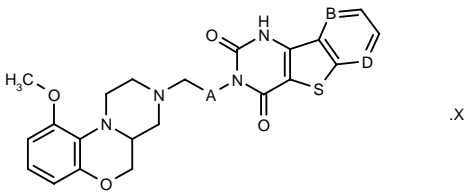
319158

(+)-3-[4-(10-Methoxy-1,2,3,4,4a,5-hexahydropyrazino[2,1-c][1,4]benzoxazin-3-yl)butyl]pyrido[2',3':4,5]thieno[3,2-d]pyrimidine-2,4(1*H*,3*H*)-dione trihydrochloride



C25 H27 N5 O4 S . 3HCl; Mol wt: 602.9680

ACTION – α_1 -Adrenoceptor antagonist with K_i values of 0.29, 0.243, 8.316 and 2.16 nM, respectively, at rat α_{1A} -, bovine α_{1A} -, hamster α_{1B} - and rat α_{1D} -adrenoceptors. Potentially useful for the treatment of benign prostatic hyperplasia, bladder outlet obstruction, neurogenic bladder and uterine smooth muscle contractions. Other exemplified benzoxazine derivatives are:



Compound	A	B	D	X	Formula
319159	-CH2-	N	CH	2HCl	C ₂₃ H ₂₃ N ₅ O ₄ S.2HCl
319160	-(CH2)2-	N	CH	3HCl	C ₂₄ H ₂₅ N ₅ O ₄ S.3HCl
319161	-(CH2)3-	CH	N	3HCl	C ₂₅ H ₂₇ N ₅ O ₄ S.3HCl

SOURCE – Abbott.

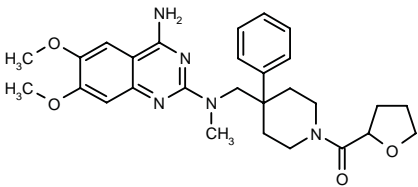
REFERENCES

1. Basha, F.Z. et al. (Abbott Laboratories) *Benzoxazine alpha-1 adrenergic cpds.* US 6376488, WO 0220533.

TREATMENT OF URINARY INCONTINENCE

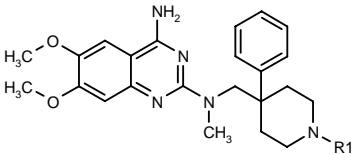
318521

1-[4-[*N*-(4-Amino-6,7-dimethoxyquinazolin-2-yl)-*N*-methylaminomethyl]-4-phenylpiperidin-1-yl]-1-(tetrahydrofuran-2-yl)methanone



C28 H35 N5 O4; Mol wt: 505.6155

ACTION – α_{1B} -Adrenoceptor antagonist, potentially useful for the treatment of urinary tract disorders such as urinary incontinence, benign prostatic hypertrophy, prostatitis, urethritis and cystitis, and also pain and CNS disorders including psychosis, paranoia, schizophrenia, attention deficiency, autism, obsessive-compulsive disorder, anorexia, bulimia, posttraumatic stress disorder, sleep disorder, bipolar disorder, convulsive disorder, depression, mania, seasonal affective disorder and anxiety. Other specifically claimed quinazoline derivatives include the following:



Compound	R1	Formula
318522	cyclopropyl-CO	C ₂₇ H ₃₃ N ₅ O ₃
318523	2,3-dihydro-1,4-benzodioxin-6-yl-CH2	C ₃₂ H ₃₇ N ₅ O ₄
318524	3-Pyr-NHCO	C ₂₉ H ₃₃ N ₇ O ₃
318525	SO2N(Me)2	C ₂₆ H ₃₄ N ₆ O ₄ S
318526	cyclopropyl-CH2C(=NH)	C ₂₈ H ₃₆ N ₆ O ₂

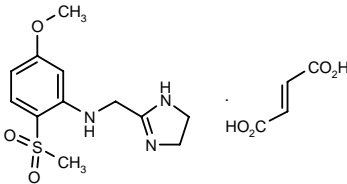
SOURCE – Roche.

REFERENCES

1. Becker, C.K. et al. (F. Hoffmann-La Roche AG) *Quinazoline derivs. as α_1 -adrenergic antagonists.* WO 0218348.

319721

N-(4,5-Dihydro-1*H*-imidazol-2-ylmethyl)-*N*-[5-methoxy-2-(methylsulfonyl)phenyl]amine fumarate



C12 H17 N3 O3 S . C4 H4 O4; Mol wt: 399.4219

ACTION – α_{1a} -Adrenoceptor agonist (pEC₅₀ = 7.85) with 250-7,000-fold functional selectivity over other α -adrenoceptor subtypes and low binding affinity for both α_1 - and α_2 -adrenoceptors (pK_i < 5.3-5.79). Potentially useful for the treatment of stress urinary incontinence.

SOURCE – GlaxoSmithKline.

REFERENCES

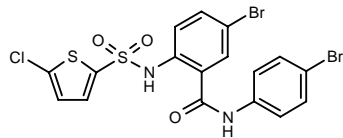
1. Bigham, E.C. et al. (GlaxoSmithKline plc) *Imidazoline derivs. as α_{1A} -adrenoceptor ligands.* EP 1175406, WO 0066563.

2. Hodson, S.J. et al. *2-(Anilinomethyl)imidazolines as α_1 -adrenergic receptor agonists: The discovery of α_{1a} subtype selective 2'-alkylsulfonyl-substituted analogues.* J Med Chem 2002, 45(11): 2229.

TREATMENT OF RENAL DISEASES

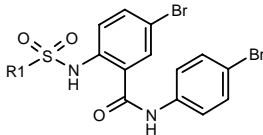
319972

5-Bromo-N-(4-bromophenyl)-2-(5-chlorothiien-2-ylsulfonamido)benzamide



C17 H11 Br2 Cl N2 O3 S2; Mol wt: 550.6779

ACTION – Phosphate transport inhibitor, particularly in the kidney and intestine. It inhibited phosphate uptake in human proximal tubule cells with an IC₅₀ of 12 μM. Potentially useful for the treatment of chronic renal failure and uremic bone disease. Other exemplified compounds are:



Compound	R1	Formula
319973	2-F-Ph	C ₁₉ H ₁₃ Br ₂ FN ₂ O ₃ S
319974	(CH ₂) ₃ Cl	C ₁₈ H ₁₅ Br ₂ ClN ₂ O ₃ S

SOURCE – GlaxoSmithKline.

REFERENCES

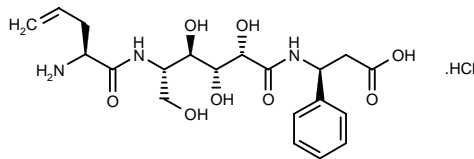
1. Weinstock, J. and Franz, R.G. (GlaxoSmithKline Inc.) *Phosphate transport inhibitors*. WO 0228353.

GASTROINTESTINAL DRUGS

ANTIULCER DRUGS

317871

3(S)-[5(S)-[2(S)-Amino-4-pentenamido]-2(S),3(R),4(R), 6-tetrahydroxyhexanamido]-3-phenylpropionic acid hydrochloride



C20 H29 N3 O8 . HCl; Mol wt: 475.9230

ACTION – Anti-*Helicobacter pylori* agent, a derivative of the natural antibiotic pyloricidin C with improved anti-bacterial activity against *H. pylori* (MIC < 0.006-0.1 and 0.39-3.13 μg/ml, respectively).

SOURCE – Takeda.

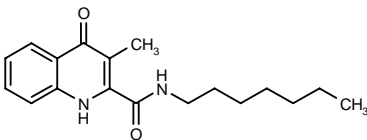
REFERENCES

1. Miyagawa, K. et al. (Takeda Chemical Industries, Ltd.) *Polyol-amino acid cpds. having anti-Helicobacter pylori activity*. EP 0998488, JP 1999080109, WO 9902549.

2. Hasuoka, A. et al. *Synthesis and anti-Helicobacter pylori activity of pyloricidin derivatives .I. Structure-activity relationships on the terminal peptidic moiety*. J Antibiot 2002, 55(3): 322.

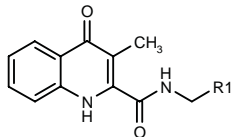
318670

N-Heptyl-3-methyl-4-oxo-1,4-dihydroquinoline-2-carboxamide



C18 H24 N2 O2; Mol wt: 300.3996

ACTION – Antibacterial agent active against *Helicobacter pylori* infections, as demonstrated *in vivo* following oral administration to rats at a dose of 1 mg/kg. Other exemplified compounds are:



Compound	R1	Formula
318671	4-Me-Ph	C ₁₉ H ₁₈ N ₂ O ₂
318673	3-MeO-Ph	C ₁₉ H ₁₈ N ₂ O ₃
318675	3-Me-PhN(Et)CH ₂	C ₂₂ H ₂₅ N ₃ O ₂

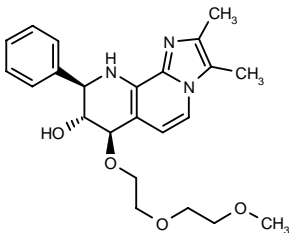
SOURCE – Yamanouchi.

REFERENCES

1. Kazami, J. et al. (Yamanouchi Pharmaceutical Co., Ltd.) *Novel ester or amide derivs*. WO 0218344.

319601

7(R)-[2-(2-Methoxyethoxy)ethoxy]-2,3-dimethyl-9(R)-phenyl-7,8,9,10-tetrahydroimidazo[1,2-*h*]-1,7-naphthyridin-8(R)-ol

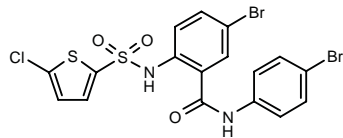


C23 H29 N3 O4; Mol wt: 411.4991

TREATMENT OF RENAL DISEASES

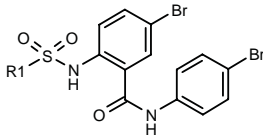
319972

5-Bromo-N-(4-bromophenyl)-2-(5-chlorothiien-2-ylsulfonamido)benzamide



C17 H11 Br2 Cl N2 O3 S2; Mol wt: 550.6779

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319974	(CH ₂) ₃ Cl	C ₁₈ H ₁₅ Br ₂ ClN ₂ O ₃ S

SOURCE – GlaxoSmithKline.

REFERENCES

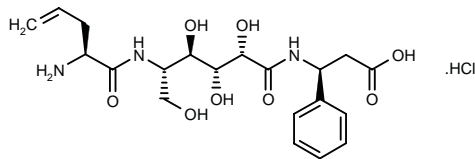
1. Weinstock, J. and Franz, R.G. (GlaxoSmithKline Inc.) *Phosphate transport inhibitors*. WO 0228353.

GASTROINTESTINAL DRUGS

ANTIULCER DRUGS

317871

3(S)-[5(S)-[2(S)-Amino-4-pentenamido]-2(S),3(R),4(R), 6-tetrahydroxyhexanamido]-3-phenylpropionic acid hydrochloride



C20 H29 N3 O8 . HCl; Mol wt: 475.9230

ACTION – Anti-*Helicobacter pylori* agent, a derivative of the natural antibiotic pyloricidin C with improved anti-bacterial activity against *H. pylori* (MIC < 0.006-0.1 and 0.39-3.13 μg/ml, respectively).

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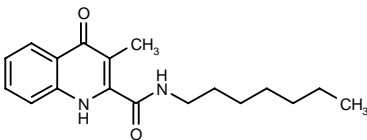
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1. Miyagawa, K. et al. (Takeda Chemical Industries, Ltd.) *Polyol-amino acid cpds. having anti-Helicobacter pylori activity*. EP 0998488, JP 1999080109, WO 9902549.

2. Hasuoka, A. et al. *Synthesis and anti-Helicobacter pylori activity of pyloricidin derivatives .I. Structure-activity relationships on the terminal peptidic moiety*. J Antibiot 2002, 55(3): 322.

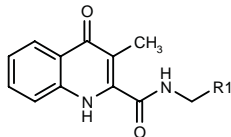
318670

N-Heptyl-3-methyl-4-oxo-1,4-dihydroquinoline-2-carboxamide



C18 H24 N2 O2; Mol wt: 300.3996

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Compound	R1	Formula
318671	4-Me-Ph	C ₁₉ H ₁₈ N ₂ O ₂
318673	3-MeO-Ph	C ₁₉ H ₁₈ N ₂ O ₃
318675	3-Me-PhN(Et)CH ₂	C ₂₂ H ₂₆ N ₂ O ₂

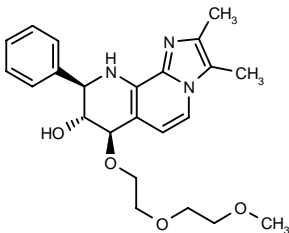
SOURCE – Yamanouchi.

REFERENCES

1. Kazami, J. et al. (Yamanouchi Pharmaceutical Co., Ltd.) *Novel ester or amide derivs*. WO 0218344.

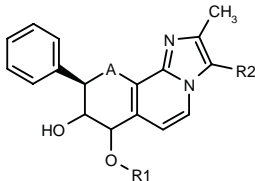
319601

7(R)-[2-(2-Methoxyethoxy)ethoxy]-2,3-dimethyl-9(R)-phenyl-7,8,9,10-tetrahydroimidazo[1,2-*h*]-1,7-naphthyridin-8(R)-ol



C23 H29 N3 O4; Mol wt: 411.4991

ACTION – Gastric antisecretory agent proven to completely prevent pentagastrin-stimulated acid secretion following intraduodenal administration to rats at 3 μmol/kg. Potentially useful for the treatment of gastro-intestinal disorders such as stomach and duodenal ulcers, gastritis and hyperacidic or drug-related functional gastropathy. Other exemplified imidazopyridines are:



Compound	R1	R2	A	Isomer	Formula
319602	CH2CH2OCH2CH2OMe	Me	NH	7S,8R	C ₂₃ H ₂₉ N ₃ O ₄
319603	H	H	NH	7R,8R	C ₁₇ H ₁₇ N ₃ O ₂
319604	CH2CH2OMe	H	NH	7S,8R	C ₂₀ H ₂₃ N ₃ O ₃
319605	CH2CH2OMe	H	NH	7R,8R	C ₂₀ H ₂₃ N ₃ O ₃
319606	CH2CH2OMe	Br	NH	7R,8R	C ₂₀ H ₂₂ BrN ₃ O ₃
319607	CH2CH2OMe	Cl	NH	7R,8R	C ₂₀ H ₂₂ ClN ₃ O ₃
319609	CH2CH2OMe	Cl	O	7R,8R	C ₂₀ H ₂₁ ClN ₂ O ₄
319610	CH2CH2OMe	H	O	7R,8R	C ₂₀ H ₂₂ N ₂ O ₄
319611	H	H	O	7R,8R	C ₁₇ H ₁₆ N ₂ O ₃
319612	Me	H	NH	7R,8R	C ₁₈ H ₁₉ N ₃ O ₂
319613	Me	H	NH	7S,8R	C ₁₈ H ₁₉ N ₃ O ₂
319614	CH2CH2OMe	CH2OH	NH	7R,8R	C ₂₁ H ₂₅ N ₃ O ₄

SOURCE – Byk Gulden (Altana Pharma).

REFERENCES

1. Simon, W.-A. et al. (Byk Gulden Lomberg Chemische Fabrik GmbH) *Polysubstd. imidazopyridines as gastric secretion inhibitors*. WO 0234749.

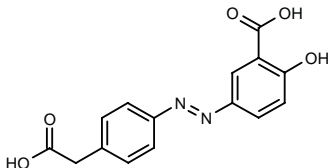
AGENTS FOR INFLAMMATORY BOWEL DISEASE

NAA-004

318530

5-[4-(Carboxymethyl)phenyldiazenyl]-2-hydroxybenzoic acid

APAZA™



C15 H12 N2 O5; Mol wt: 300.2688

ACTION – A representative compound from a series of immunomodulators with potential in the treatment of inflammatory disorders of the gastrointestinal tract, particularly inflammatory bowel disease. The compound underwent bacterial reduction to yield 5-aminosalicylic acid (5-ASA) and 4-aminophenylacetic acid (4-APAA) following oral administration to rats. In addition, treatment with the combination of the two APAZA metabolites was shown to be effective in a rat model of DNBS-induced colitis.

SOURCE – Nobex.

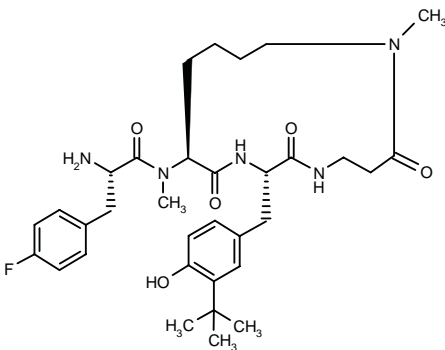
REFERENCES

1. Ekwuribe, N.N. and Riggs-Sauthier, J. (Nobex Corp.) *Immunoregulatory cpds. and derivs. and methods of treating diseases therewith*. WO 0218324.
2. *Product Pipeline*. Nobex Website. June 04, 2002.

ANTIDIARRHEAL AGENTS

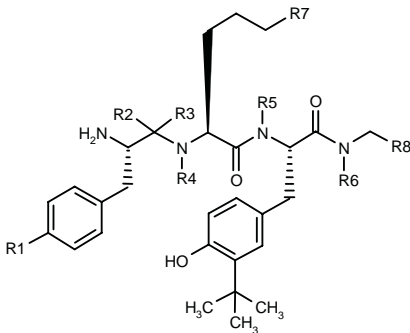
318495

4-Fluoro-L-phenylalanyl-*N*²,*N*⁶-dimethyl-L-lysyl-3-*tert*-butyl-L-tyrosyl-β-alanine C-1.4-*N*-6.2-lactam



C33 H46 F N5 O5; Mol wt: 611.7544

ACTION – Motilin receptor antagonist for the treatment of digestive hypermotility. Compound inhibited the binding of [¹²⁵I]-motilin to motilin receptors in rabbit duodenal mucosa with an IC₅₀ of 1.4 nM, and prevented acetylcholine-induced contractions in rabbit duodenal longitudinal muscle preparations with a pA₂ of 9.9. Other exemplified cyclic peptides include the following:



Compound	R1	R2	R3	R4	R5	R6	R7	R8	Formula
318497	F	-O-	Me	H	H		-CH2NHCOCH2-		C ₃₂ H ₄₄ FN ₅ O ₅
318498	F	-O-	Me	Me	H		-CH2NHCOCH2-		C ₃₃ H ₄₆ FN ₅ O ₅
318499	F	-O-	Me	H	H		-CH2NHCO-		C ₃₁ H ₄₂ FN ₅ O ₅
318500	F	-O-	Me	H	Me		-CH2NHCOCH2-		C ₃₃ H ₄₆ FN ₅ O ₅
318503	F	-O-	Me	H	H		-CH2NHCOCH2CH2-		C ₃₃ H ₄₆ FN ₅ O ₅
318505	F	H	H	H	H		-CH2NHCOCH2-		C ₃₁ H ₄₄ FN ₅ O ₄
318508	F	-O-	Me	H	H		-CH2N(Ac)CH2CH2-		C ₃₄ H ₄₈ FN ₅ O ₅
318509	F	-O-	Me	H	H		-N(Me)COCH2CH2-		C ₃₃ H ₄₆ FN ₅ O ₅
318511	H	-O-	Me	H	H		-CH2NHCOCH2-		C ₃₂ H ₄₈ N ₆ O ₅

SOURCE – Chugai.

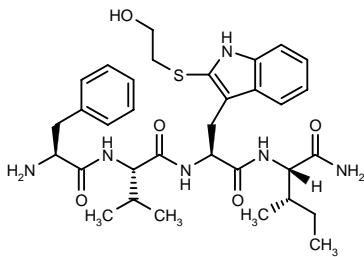
REFERENCES

1. Matsuoka, H. and Sato, T. (Chugai Pharmaceutical Co. Ltd.) *Cyclic peptide deriv.* WO 0216404.

TREATMENT OF DISORDERS OF GASTRIC EMPTYING

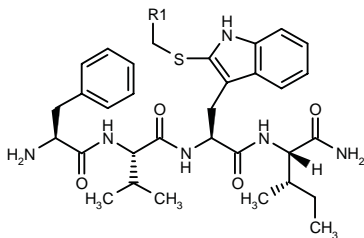
319292

L-Phenylalanyl-L-valyl-2’-(2-hydroxyethylsulfanyl)-L-tryptophyl-L-isoleucinamide



C33 H46 N6 O5 S; Mol wt: 638.8294

ACTION– Motilin agonist giving an EC₅₀ value of 14.1 μM for inducing contractions of rabbit duodenal smooth muscle and nanomolar binding affinity for rabbit motilin receptors (IC₅₀ = 0.57 μM). Potential prokinetic agent for the treatment of patients with hypomotility syndromes. Other motilin *N*-terminal tetrapeptide derivatives are:



Compound	R1	Formula
319294	H	C ₃₂ H ₄₄ N ₆ O ₄ S
319295	Et	C ₃₄ H ₄₈ N ₆ O ₄ S

SOURCE – Chugai.

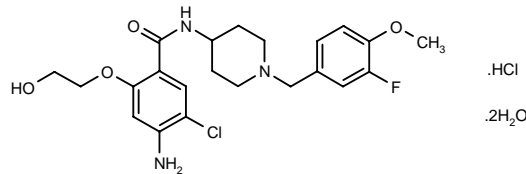
REFERENCES

1. Haramura, M. et al. *Design and synthesis of novel tetra-peptide motilin agonists.* Bioorg Med Chem 2002, 10(6): 1805.

KDR-5169*

305448

4-Amino-5-chloro-*N*-[1-(3-fluoro-4-methoxybenzyl)piperidin-4-yl]-2-(2-hydroxyethoxy)benzamide hydrochloride dihydrate



C22 H27 Cl F N3 O4 . HCl . 2H2O; Mol wt: 524.4138

ACTION– Gastrointestinal prokinetic agent with affinity for rat brain D2 receptors (K_i = 6.2 nM) and guinea pig brain 5-HT₄ receptors (K_i = 81 nM), agonist activity at 5-HT₄ receptors (EC₅₀ = 61 nM in tunica muscularis mucosae preparations from rat esophagus) and dopamine-antagonist activity. In conscious dogs, doses of 0.3-1 mg/kg i.v. stimulated upper gastrointestinal tract motility and reversed both the suppression of gastrointestinal motor activity and the induction of emesis seen following postprandial L-DOPA infusion. Compound was effective in rats against quinpirole-induced gastroparesis, postoperative ileus and surgery/quinpirole-induced gastroparesis, whereas the reference compounds cisapride, domperidone and mosapride were active only in specific models. Potentially useful for the treatment of various forms of gastric ileus.

SOURCE – Kissei.

REFERENCES

1. Okazaki, K. et al. (Kissei Pharmaceutical Co., Ltd.) *Hydroxyethoxybenzamide derivs. and drugs containing the same.* WO 0136385.
2. Tazawa, S. et al. *KDR-5169, a new gastrointestinal prokinetic agent, enhances gastric contractile and emptying activities in dogs and rats.* Eur J Pharmacol 2002, 434(3): 169.

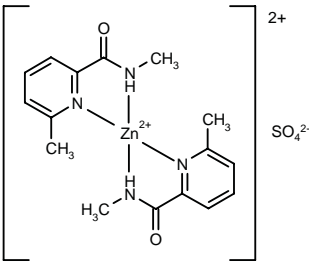
*Identified compound **305448** Drug Data Rep 2001, 023(10): 0989.

ENDOCRINE DRUGS

ANTIDIABETIC DRUGS

317205

[Bis(*N*,6-dimethylpyridine-2-carboxamide)zinc sulfate



C16 H20 N4 O6 S Zn; Mol wt: 461.8120

SOURCE – Chugai.

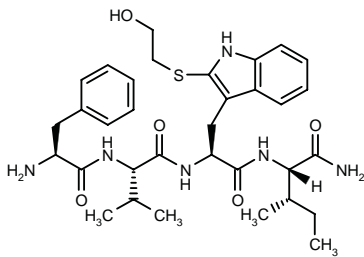
REFERENCES

1. Matsuoka, H. and Sato, T. (Chugai Pharmaceutical Co. Ltd.) *Cyclic peptide deriv.* WO 0216404.

TREATMENT OF DISORDERS OF GASTRIC EMPTYING

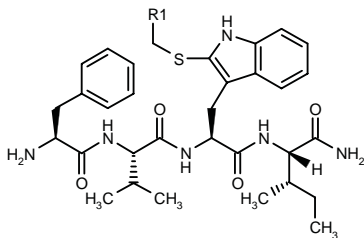
319292

L-Phenylalanyl-L-valyl-2’-(2-hydroxyethylsulfanyl)-L-tryptophyl-L-isoleucinamide



C33 H46 N6 O5 S; Mol wt: 638.8294

ACTION – Motilin agonist giving an EC₅₀ value of 14.1 μM for inducing contractions of rabbit duodenal smooth muscle and nanomolar binding affinity for rabbit motilin receptors (IC₅₀ = 0.57 μM). Potential prokinetic agent for the treatment of patients with hypomotility syndromes. Other motilin *N*-terminal tetrapeptide derivatives are:



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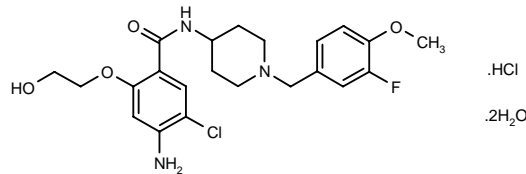
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KDR-5169*

305448

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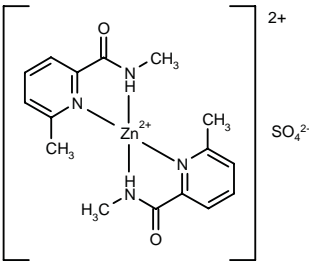
*Identified compound **305448** Drug Data Rep 2001, 023(10): 0989.

ENDOCRINE DRUGS

ANTIDIABETIC DRUGS

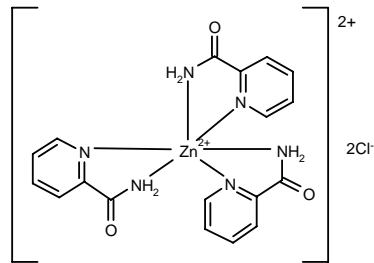
317205

[Bis(*N*,6-dimethylpyridine-2-carboxamide)zinc sulfate



C16 H20 N4 O6 S Zn; Mol wt: 461.8120

ACTION – Insulinomimetic agent, a Zn(II) complex with a picolinamide derivative able to inhibit epinephrine-induced free fatty acid release from isolated rat adipocytes with an IC₅₀ value of 0.97 mM. In the KKA^y mouse model of type 2 diabetes, a dose of 4 mg/kg/day i.p. for 14 days normalized blood glucose levels without symptoms of liver or renal toxicity. Potentially useful for the treatment of type 2 diabetes.



317204: C18 H18 Cl2 N6 O3 Zn

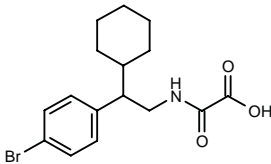
SOURCES – Kyoto Pharmaceutical University, Kyoto (JP); Osaka City University, Osaka (JP); Osaka Municipal Technical Research Institute, Osaka (JP).

REFERENCES

1. Ueda, E. et al. *Potential insulinomimetic agents of zinc(II) complexes with picolinamide derivatives: Preparations of complexes, in vitro and in vivo studies.* Chem Pharm Bull 2002, 50(3): 337.

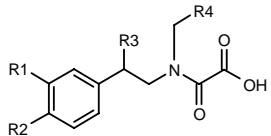
318339

N-[2-(4-Bromophenyl)-2-cyclohexylethyl]oxamic acid

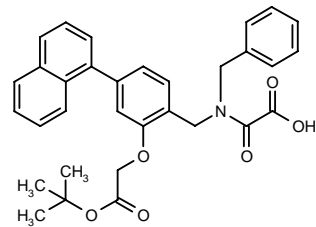


C16 H20 Br N O3; Mol wt: 354.2420

ACTION – Protein-tyrosine-phosphatase PTP1B inhibitor for use in the treatment of type 2 diabetes and obesity. Other specifically claimed compounds include the following:



Compound	R1	R2	R3	R4	Formula
318342	H	1-Naph	cyclohexyl	Ph	C ₃₃ H ₃₃ NO ₃
318345	H	SO ₂ NH-COCO ₂ H	H	4-(1-Naph)-PhCH(cyclohexyl)	C ₃₆ H ₃₆ N ₂ O ₈ S
318347	H	3-Ph-Ph	cyclohexyl	Ph	C ₃₅ H ₃₅ NO ₃
318348	H	1-Naph	1-(PhCO)-4-Pip	CH ₂ Ph	C ₄₀ H ₃₈ N ₂ O ₄
318349	H	4-Ph-PhNH-COCH=CH	cyclohexyl	Ph	C ₃₈ H ₃₈ N ₂ O ₄
318350	Ph	H	cyclohexyl	CH ₂ Ph	C ₃₀ H ₃₃ NO ₃
318353	3-Ph-Ph	H	cyclohexyl	CH ₂ Ph	C ₃₆ H ₃₇ NO ₃



318343: C32 H31 N O6

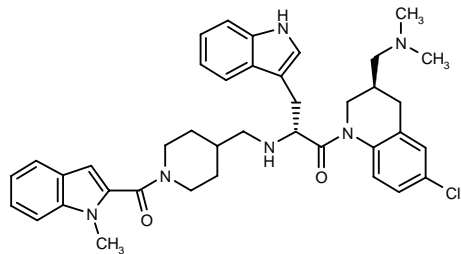
SOURCE – Abbott.

REFERENCES

1. Liu, G. et al. (Abbott Laboratories) *Amino(oxo)acetic acid protein tyrosine phosphatase inhibitors.* WO 0218321.

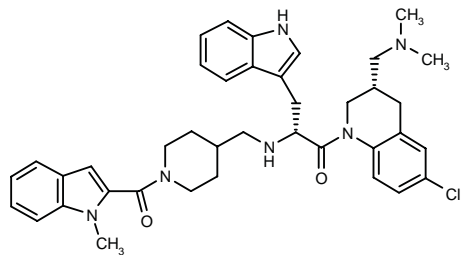
318439

N-[6-Chloro-1-[N-[1-(1-methyl-1H-indol-2-ylcarbonyl)-piperidin-4-ylmethyl]-D-tryptophyl]-1,2,3,4-tetrahydroquinolin-3(R)-ylmethyl]-N,N-dimethylamine



C39 H45 Cl N6 O2; Mol wt: 665.2775

ACTION – Somatostatin receptor antagonist giving an IC₅₀ value of 0.08 nM at somatostatin sst₂ receptors in binding assays, with > 1,000 and > 6,000-fold selectivity, respectively, over sst₃ and sst₅ receptor subtypes. Potentially useful for the treatment of diabetes and complications related therewith. Another exemplified amine derivative is:



318440: C39 H45 Cl N6 O2

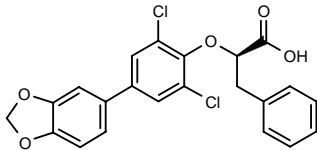
SOURCE – Takeda.

REFERENCES

1. Abe, H. et al. (Takeda Chemical Industries, Ltd.) *Amine derivs.* WO 0216350.

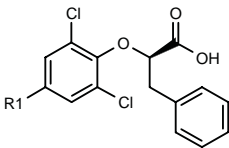
318448

2(*R*)-[4-(1,3-Benzodioxol-5-yl)-2,6-dichlorophenoxy]-3-phenylpropionic acid



C22 H16 Cl2 O5; Mol wt: 431.2694

ACTION – Protein-tyrosine-phosphatase PTP1B inhibitor, potentially useful for the treatment of type 2 diabetes and obesity. Other specifically claimed compounds are:



Compound	R1	Formula
318457	5-indolyl	C ₂₃ H ₁₇ Cl ₂ NO ₃
318458	4-(CF ₃ O)-Ph	C ₂₂ H ₁₅ Cl ₂ F ₃ O ₄
318460	1-thianthrenyl	C ₂₇ H ₁₈ Cl ₂ O ₃ S ₂

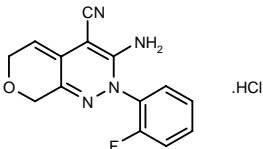
SOURCE – Abbott.

REFERENCES

1. Liu, G. and Pei, Z.H. (Abbott Laboratories) *Protein tyrosine phosphatase inhibitors*. WO 0218363.

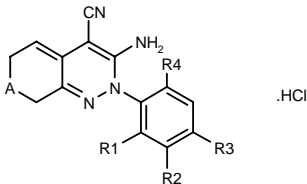
318579

3-Amino-2-(2-fluorophenyl)-6,8-dihydro-2*H*-pyrano[3,4-*c*]-pyridazine-4-carbonitrile hydrochloride

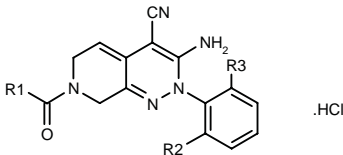


C14 H11 F N4 O . HCl; Mol wt: 306.7268

ACTION – Protein-tyrosine-phosphatase inhibitor, considered to have potential in the treatment of type 2 diabetes. Other specifically claimed bicyclic 3-amino-4-cyano-pyridazine derivatives include the following:



Compound	R1	R2	R3	R4	A	Formula
318581	H	H	H	H	S	C ₁₄ H ₁₂ N ₄ S.HCl
318582	H	Cl	Cl	H	O	C ₁₄ H ₁₀ Cl ₂ N ₄ O.HCl
318585	F	H	H	Cl	O	C ₁₄ H ₁₀ ClFN ₄ O.HCl
318586	H	H	N(Me)2	H	O	C ₁₆ H ₁₇ N ₅ O.HCl
318587	Me	H	Me	Me	O	C ₁₇ H ₁₈ N ₄ O.HCl
318591	t-Bu	H	H	H	O	C ₁₈ H ₂₀ N ₄ O.HCl



Compound	R1	R2	R3	Formula
318584	Me	Me	Me	C ₁₈ H ₁₉ N ₅ O.HCl
318589	OCH2Ph	H	H	C ₂₂ H ₁₉ N ₅ O ₂ .HCl

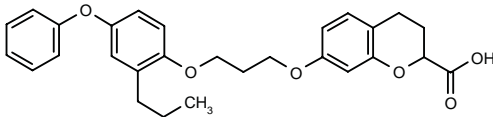
SOURCE – Biovitrum.

REFERENCES

1. Barker, E. et al. (Biovitrum AB) *Novel pyridazine cpds. for the treatment of diabetes*. WO 0226743.

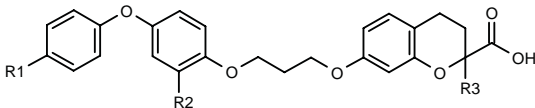
318903

7-[3-(4-Phenoxy-2-propylphenoxy)propoxy]-3,4-dihydro-2*H*-1-benzopyran-2-carboxylic acid

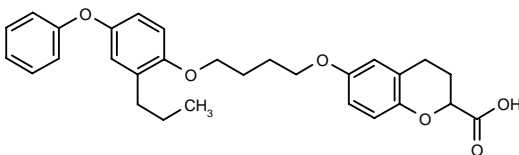


C28 H30 O6; Mol wt: 462.5390

ACTION – Peroxisome proliferator-activated receptor PPARα and/or PPARγ agonist, potentially useful for the treatment of type 2 diabetes, hyperglycemia, hyperlipidemia, hypertriglyceridemia and hypercholesterolemia, obesity, dyslipidemia, atherosclerosis and cachexia. Other exemplified 3,4-dihydro-2*H*-1-benzopyran-2-carboxylic acid derivatives are:



Compound	R1	R2	R3	Isomer	Formula
318906	Cl	Pr	Et		C ₃₀ H ₃₃ ClO ₆
318907	i-Bu	Pr	Et		C ₃₄ H ₄₂ O ₆
318909	H	Cl	Me		C ₂₆ H ₂₅ ClO ₆
318910	F	Cl	H		C ₂₅ H ₂₂ ClFO ₆
318911	H	F	Et		C ₂₇ H ₂₇ FO ₆
318912	F	Cl	Et	R	C ₂₇ H ₂₆ ClFO ₆
318913	i-Bu	Pr	Pr	R	C ₃₅ H ₄₄ O ₆



318908: C29 H32 O6

SOURCE – Merck & Co.

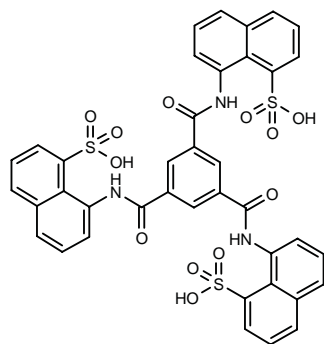
REFERENCES

1. Sahoo, S.P. et al. (Merck & Co., Inc.) *Benzopyrancarboxylic acid derivs. for the treatment of diabetes and lipid disorders*. WO 0226729.

318985

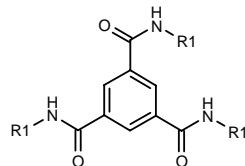
8,8',8''-(Benzene-1,3,5-triyl)tris(carbonyl)tris(imino)-tris(naphthalene-1-sulfonic acid)

N,N',N''-Tris(8-sulfonaphthalen-1-yl)benzene-1,3,5-tricarboxamide



C39 H27 N3 O12 S3; Mol wt: 825.8493

ACTION – Agent with the ability to enhance insulin-dependent glucose uptake through stimulation of insulin receptor kinase activity. This compound was shown to increase autophosphorylation of the β -kinase domain of the human insulin receptor (CKD) *in vitro* and it also demonstrated glucose transport-stimulating activity in 3T3 L1 fibroblasts at a concentration of 3.2 μ M. Potentially useful for the treatment of hyperglycemia and type 1 and type 2 diabetes. Other exemplified benzene-1,3,5-tricarboxylic acid derivatives are:



Compound	R1	Formula
318987	6-SO3H-1-Naph	C ₃₉ H ₂₇ N ₃ O ₁₂ S ₃
318991	7-SO3H-1-Naph	C ₃₉ H ₂₇ N ₃ O ₁₂ S ₃
318993	6-SO3H-2-Naph	C ₃₉ H ₂₇ N ₃ O ₁₂ S ₃
318994	5-SO3H-2-Naph	C ₃₉ H ₂₇ N ₃ O ₁₂ S ₃

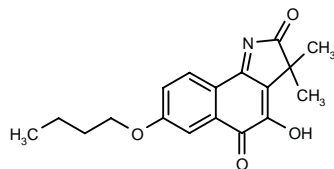
SOURCE – Telik.

REFERENCES

1. Robinson, L. et al. (Telik, Inc.) *Benzene tricarboxylic acid derivs. as insulin receptor activators*. WO 0220464.

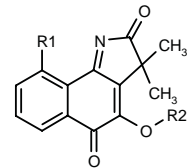
319113

7-Butoxy-4-hydroxy-3,3-dimethyl-3,5-dihydro-2*H*-benzo[*g*]indole-2,5-dione

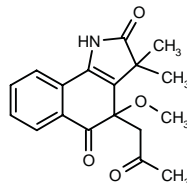


C18 H19 N O4; Mol wt: 313.3511

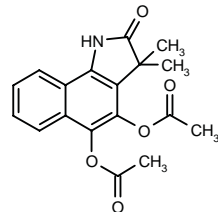
ACTION – Protein-tyrosine-phosphatase (PTP) inhibitor for use in the treatment of type 2 diabetes. Other specifically claimed benzo[*g*]indole-2-one derivatives are:



Compound	R1	R2	Formula
319114	OCH2Ph	H	C ₂₁ H ₁₇ NO ₄
319115	i-BuO	H	C ₁₈ H ₁₉ NO ₄
319116	OCH2CH2Ph	H	C ₂₂ H ₁₉ NO ₄
319117	OEt	H	C ₁₆ H ₁₅ NO ₄
319118	OCH2CONH2	H	C ₁₆ H ₁₄ N ₂ O ₅
319119	H	Me	C ₁₅ H ₁₃ NO ₃



319120: C18 H19 N O4



319121: C18 H17 N O5

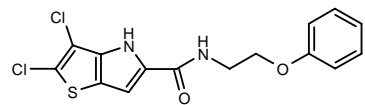
SOURCE – Biovitrum.

REFERENCES

1. Byström, S. et al. (Biovitrum AB) *Novel cpds*. US 2002061921, WO 0226707.

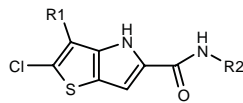
319162

2,3-Dichloro-*N*-(2-phenoxyethyl)-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide



C15 H12 Cl2 N2 O2 S; Mol wt: 355.2438

ACTION – Agent with glycogen phosphorylase-inhibitory activity, potentially useful for the treatment of type 2 diabetes, as well as insulin resistance, diabetic neuropathy, diabetic nephropathy, diabetic retinopathy, cataracts, hyperglycemia, hypercholesterolemia, hypertension, hyperinsulinemia, hyperlipidemia, atherosclerosis, cardiac ischemia, syndrome X and obesity. Other exemplified compounds include the following:



Compound	R1	R2	Formula
319163	H	CH2COPh	C ₁₅ H ₁₁ ClN ₂ O ₂ S
319164	Cl	CH(CH2OH)CH2Ph	C ₁₆ H ₁₄ Cl ₂ N ₂ O ₂ S
319165	Cl	4-(AcNH)-PhOCH2CH(OH)CH2	C ₁₈ H ₁₇ Cl ₂ N ₃ O ₄ S
319166	Cl	CH2CONHCH2Ph	C ₁₆ H ₁₃ Cl ₂ N ₃ O ₂ S
319167	Cl	CH2CON(Me)CH2CH2OH	C ₁₂ H ₁₃ Cl ₂ N ₃ O ₃ S
319168	Cl	CH2CON(i-Pr)Me	C ₁₃ H ₁₅ Cl ₂ N ₃ O ₂ S
319169	Cl	2-(PhCH2NHCOCH2O)-PhCH2CH2	C ₂₄ H ₂₁ Cl ₂ N ₃ O ₃ S
319171	Cl	1-NH2-2-indanyl	C ₁₆ H ₁₃ Cl ₂ N ₃ OS

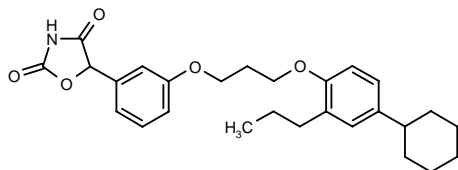
SOURCE – AstraZeneca.

REFERENCES

1. Bartlett, J.B. et al. (AstraZeneca AB) *Bicyclic pyrrolyl amides as glycogen phosphorylase inhibitors*. WO 0220530.

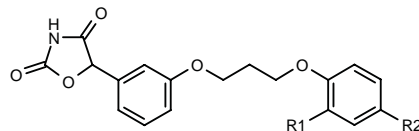
319586

5-[3-[3-(4-Cyclohexyl-2-propylphenoxy)propoxy]phenyl]-oxazolidine-2,4-dione



C27 H33 N O5; Mol wt: 451.5597

ACTION – Potent peroxisome proliferator-activated receptor PPAR agonist for use in the treatment of diabetes, obesity, hyperglycemia, hyperlipidemia, hypercholesterolemia, hypertriglyceridemia and dyslipidemia. Other specifically claimed oxazolidine-2,4-dione derivatives are:



Compound	R1	R2	Formula
319587	Pr	cyclopentyl	C ₂₆ H ₃₁ NO ₅
319588	Cl	cyclopentyl	C ₂₃ H ₂₄ ClNO ₅
319589	Pr	4,4-(F)2-cyclohexyl	C ₂₇ H ₃₁ F ₂ NO ₅
319590	Cl	4,4-(F)2-cyclohexyl	C ₂₄ H ₂₄ ClF ₂ NO ₅
319591	Pr	4,4-(Me)2-cyclohexyl	C ₂₉ H ₃₇ NO ₅
319592	Cl	4,4-(Me)2-cyclohexyl	C ₂₆ H ₃₀ ClNO ₅
319593	Pr	4-morpholinyl	C ₂₅ H ₃₀ N ₂ O ₆
319594	Pr	4-THP	C ₂₆ H ₃₁ NO ₆
319595	Cl	4-THP	C ₂₃ H ₂₄ ClNO ₆

SOURCE – Merck & Co.

REFERENCES

1. Desai, R.C. et al. (Merck & Co., Inc.) *Arylthiazolidinedione and aryloxazolidinedione derivs*. US 6380191.

BAY-55-9837

305039

L-Histidyl-L-seryl-L-aspartyl-L-alanyl-L-valyl-L-phenylalanyl-L-threonyl-L-aspartyl-L-asparaginyll-L-tyrosyl-L-threonyl-L-arginyl-L-leucyl-L-arginyl-L-lysyl-L-glutaminyll-L-valyl-L-alanyl-L-alanyl-L-lysyl-L-lysyl-L-tyrosyl-L-leucyl-L-glutaminyll-L-seryl-L-isoleucyl-L-lysyl-L-asparaginyll-L-lysyl-L-arginyl-L-tyrosine

C167 H269 N51 O47; Mol wt: 3743.2720

ACTION – Potent and selective agonist at the shared vasoactive intestinal peptide (VIP) and pituitary adenylate cyclase-activating peptide (PACAP) receptor VAPC₂ with high selectivity for VAPC₂ over VAPC₁ receptors (IC₅₀ = 60 and 8700 nM, respectively) and no activity at the PAC₁ receptor at up to 10 µM. It displayed full agonist activity at the human VPAC₂ receptor (EC₅₀ = 0.4 nM). In isolated rat and human pancreatic islets, compound produced concentration- and glucose-dependent increases in insulin secretion; stimulation of insulin synthesis was observed in rat islets. In fasted rats, it dose-dependently increased plasma insulin with an ED₅₀ value of approximately 3 pmol/kg i.v.; continuous i.v. (1-100 pmol/kg/min) or s.c. (3, 30 and 300 pmol/kg/min) infusion of compound reduced the glucose AUC following an i.p. glucose tolerance test. Gastrointestinal and cardiovascular side effects (watery diarrhea and peripheral vasodilatation) were observed only at high doses in rats. Potentially useful for the treatment of type 2 diabetes.

SOURCE – Bayer.

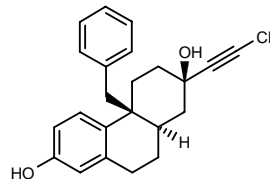
REFERENCES

1. Pan, C. et al. *Engineering of the VPAC2-selective agonist BAY 55-9837 for the treatment of type 2 diabetes*. Diabetes 2001, 50(Suppl. 2): Abst 943-P.
2. Tsutsumi, M. et al. *A potent and highly selective VPAC2 agonist enhances glucose-induced insulin release and glucose disposal. A potential therapy for type 2 diabetes*. Diabetes 2002, 51(5): 1453.

CP-394531

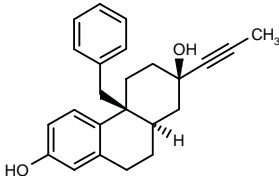
319375

(2*R*,4*aS*,10*aR*)-4*a*-Benzyl-2-(chloroethynyl)-1,2,3,4,4*a*,9,10,10*a*-octahydrophenanthrene-2,7-diol



C23 H23 Cl O2; Mol wt: 366.8857

ACTION – Potent, nonsteroidal glucocorticoid receptor (GR) antagonist with subnanomolar affinity for GR receptors ($K_i = 0.1$ nM) and high selectivity over human progesterone, androgen and estrogen receptors. Compound exhibited potent functional antagonist activity at human GR receptors and produced complete inhibition of the half-maximal agonist response to dexamethasone at a concentration of 1 μ M; no agonist activity or functional activity versus other human steroid receptors was seen. Potentially useful for the treatment of diabetes, obesity, depression, neurodegeneration, glaucoma and Cushing’s disease. Another related compound is:



CP-409069 [319374]: C24 H26 O2

SOURCE – Pfizer.

REFERENCES

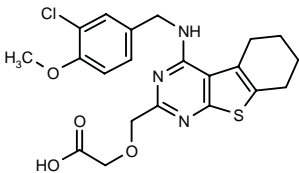
1. Dow, R.L. et al. (Pfizer Products Inc.) *Glucocorticoid receptor modulators*. EP 1175383, US 6380223, WO 0066522.

2. Morgan, B.P. et al. *Discovery of potent, nonsteroidal, and highly selective glucocorticoid receptor antagonists*. J Med Chem 2002, 45(12): 2417.

TREATMENT OF MALE SEXUAL DYSFUNCTION

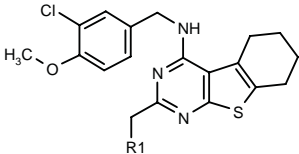
318474

2-[4-(3-Chloro-4-methoxybenzylamino)-5,6,7,8-tetrahydro[1]benzothieno[2,3-d]pyrimidin-2-ylmethoxy]acetic acid



C21 H22 Cl N3 O4 S; Mol wt: 447.9408

ACTION – Phosphodiesterase type 5 (PDE5) inhibitor potentially useful for the treatment of angina, hypertension, pulmonary hypertension, congestive heart failure, atherosclerosis, peripheral vascular diseases, stroke, bronchitis, asthma, allergic rhinitis, glaucoma, irritable bowel syndrome, cancer, renal insufficiency, liver cirrhosis and female sexual disorders. Other specifically claimed thienopyrimidine derivatives are:



Compound	R1	Formula
318475	SCH2CO2H	C ₂₁ H ₂₂ ClN ₃ O ₃ S ₂
318476	SOCH2CO2H	C ₂₁ H ₂₂ ClN ₃ O ₄ S ₂
318477	CH2OCH2CO2H	C ₂₂ H ₂₄ ClN ₃ O ₄ S

SOURCE – Merck KGaA.

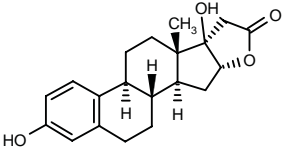
REFERENCES

1. Jonas, R. et al. (Merck Patent GmbH) *Thienopyrimidine*. DE 10042997, WO 0218389.

TREATMENT OF GYNECOLOGICAL DISORDERS

318705

3,16 α ,17 β -Trihydroxy-19-nor-pregna-1,3,5(10)-trien-21-carboxylic acid γ -lactone



C20 H24 O4; Mol wt: 328.4056

ACTION – A representative compound from a series of 19-norpregna-1,3,5(10)-triene-21,16 α -lactones with affinity for estrogen ER α receptors. Compound displayed affinity for ERs in rat uterine preparations but not in rat prostate preparations. It was shown to induce an increase in uterine weight when administered to ovariectomized rats. Potentially useful as a contraceptive and for hormone replacement therapy in the treatment of estrogen-related disorders including postmenopausal syndrome, ovarian dysfunction, osteoporosis, cardiovascular disorders such as atherosclerosis, neurodegenerative diseases such as Alzheimer’s disease, autoimmune disorders such as rheumatoid arthritis, for wound healing and prostate cancer.

SOURCE – Jenapharm.

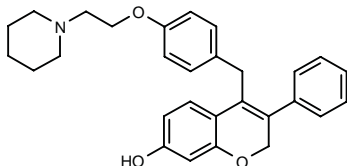
REFERENCES

1. Müller, G. et al. (Jenapharm GmbH) *19-Nor-17 α -pregna-1,3,5(10)-trien-17 β -ols of a 21,16 α -lactone ring*. WO 0226763.

CHF-4056

312229

3-Phenyl-4-[4-[2-(1-piperidinyl)ethoxy]benzyl]-2H-1-benzopyran-7-ol



C29 H31 N O3; Mol wt: 441.5679

ACTION – Nonsteroidal selective estrogen receptor modulator (SERM) with high affinity for human estrogen receptors ER α and ER β (K_i = 0.041 and 0.157 nM, respectively). In immature rats, compound fully antagonized the 17 α -ethinylestradiol-induced increase in uterine weight with an ED₅₀ value of 0.33 mg/kg/day p.o., while it lacked uterine stimulant activity; in this test, levormeloxifene significantly increased uterine weight, acting as a partial agonist. In ovariectomized rats, compound (0.1-1 mg/kg/day p.o. for 4 weeks) significantly attenuated bone loss in the lumbar spine and the increase in serum osteocalcin, and it also significantly reduced total serum cholesterol levels with an ED₅₀ of 0.12 mg/kg/day. Its potential for the treatment of estrogen-dependent tumors such as breast cancer is also under study.

SOURCE – Chiesi.

REFERENCES

1. Galbiati, E. et al. *Effects of 3-phenyl-4-[[4-[2-(1-piperidinyl)ethoxy]phenyl]methyl]-2H-1-benzopyran-7-ol (CHF 4056), a novel nonsteroidal estrogen agonist/antagonist, on reproductive and nonreproductive tissue.* J Pharmacol Exp Ther 2002, 300(3): 802.

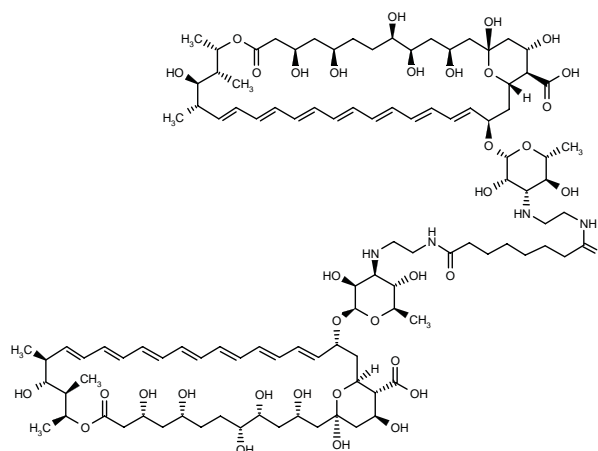
2. *R&D pipeline.* Chiesi Group Web Site 2001, Dec 11.

ANTIINFECTIVE THERAPY

ANTIBIOTICS

318834

N,N'-(Hexane-1,6-diyl)bis(carbonyl)bis(iminoethylene)bis-[(1*R*,3*S*,5*R*,6*R*,9*R*,11*R*,15*S*,16*R*,17*R*,18*S*,19*E*,21*E*,23*E*,25*E*,27*E*,29*E*,31*E*,33*R*,35*S*,36*R*,37*S*)-33-(3-amino-3,6-dideoxy- β -D-mannopyranosyloxy)-1,3,5,6,9,11,17,37-octahydroxy-15,16,18-trimethyl-13-oxo-14,39-dioxabicyclo[33.3.1]nonatriaconta-19,21,23,25,27,29,31-heptaene-36-carboxylic acid]



C106 H166 N4 O36; Mol wt: 2072.4690

ACTION – Oligomeric macrolide antibiotic with improved selectivity and antifungal activity. It proved active *in vitro* against *Aspergillus niger* and gave an EC₅₀ of 1.1 μ M when tested for hemolytic activity using human erythrocytes.

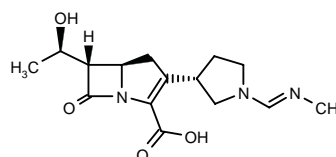
SOURCE – Japan Science and Technology.

REFERENCES

1. Murata, M. and Matsumori, N. (Japan Science and Technology Corp.) *Polymer of polyene macrolide antibiotics.* JP 2002069091.

319087

(5*R*,6*S*)-6-[1(*R*)-Hydroxyethyl]-3-[1-(methyliminomethyl)-pyrrolidin-3(*S*)-yl]-1-carbapen-2-em-3-carboxylic acid



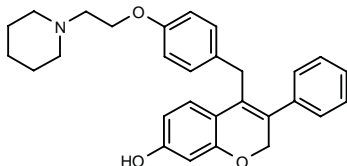
C15 H21 N3 O4; Mol wt: 307.3479

ACTION – Carbapenem antibiotic with good antibacterial activity against *Staphylococcus aureus* and *Pseudomonas aeruginosa* and good stability towards the renal enzyme dehydropeptidase I (DHP-I).

CHF-4056

312229

3-Phenyl-4-[4-[2-(1-piperidinyl)ethoxy]benzyl]-2H-1-benzopyran-7-ol



C29 H31 N O3; Mol wt: 441.5679

ACTION – Nonsteroidal selective estrogen receptor modulator (SERM) with high affinity for human estrogen receptors ER α and ER β (K_i = 0.041 and 0.157 nM, respectively). In immature rats, compound fully antagonized the 17 α -ethinylestradiol-induced increase in uterine weight with an ED₅₀ value of 0.33 mg/kg/day p.o., while it lacked uterine stimulant activity; in this test, levormeloxifene significantly increased uterine weight, acting as a partial agonist. In ovariectomized rats, compound (0.1-1 mg/kg/day p.o. for 4 weeks) significantly attenuated bone loss in the lumbar spine and the increase in serum osteocalcin, and it also significantly reduced total serum cholesterol levels with an ED₅₀ of 0.12 mg/kg/day. Its potential for the treatment of estrogen-dependent tumors such as breast cancer is also under study.

SOURCE – Chiesi.

REFERENCES

1. Galbiati, E. et al. *Effects of 3-phenyl-4-[[4-[2-(1-piperidinyl)ethoxy]phenyl]methyl]-2H-1-benzopyran-7-ol (CHF 4056), a novel nonsteroidal estrogen agonist/antagonist, on reproductive and nonreproductive tissue.* J Pharmacol Exp Ther 2002, 300(3): 802.

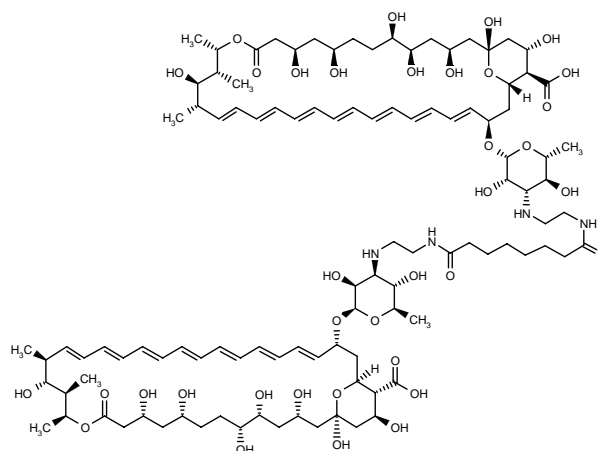
2. *R&D pipeline.* Chiesi Group Web Site 2001, Dec 11.

ANTIINFECTIVE THERAPY

ANTIBIOTICS

318834

N,N'-(Hexane-1,6-diyl)bis(carbonyl)bis(iminoethylene)bis-[(1*R*,3*S*,5*R*,6*R*,9*R*,11*R*,15*S*,16*R*,17*R*,18*S*,19*E*,21*E*,23*E*,25*E*,27*E*,29*E*,31*E*,33*R*,35*S*,36*R*,37*S*)-33-(3-amino-3,6-dideoxy- β -D-mannopyranosyloxy)-1,3,5,6,9,11,17,37-octahydroxy-15,16,18-trimethyl-13-oxo-14,39-dioxabicyclo[33.3.1]nonatriaconta-19,21,23,25,27,29,31-heptaene-36-carboxylic acid]



C106 H166 N4 O36; Mol wt: 2072.4690

ACTION – Oligomeric macrolide antibiotic with improved selectivity and antifungal activity. It proved active *in vitro* against *Aspergillus niger* and gave an EC₅₀ of 1.1 μ M when tested for hemolytic activity using human erythrocytes.

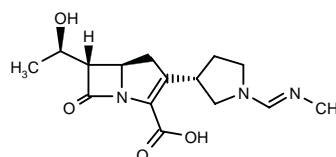
SOURCE – Japan Science and Technology.

REFERENCES

1. Murata, M. and Matsumori, N. (Japan Science and Technology Corp.) *Polymer of polyene macrolide antibiotics.* JP 2002069091.

319087

(5*R*,6*S*)-6-[1(*R*)-Hydroxyethyl]-3-[1-(methyliminomethyl)-pyrrolidin-3(*S*)-yl]-1-carbapen-2-em-3-carboxylic acid



C15 H21 N3 O4; Mol wt: 307.3479

ACTION – Carbapenem antibiotic with good antibacterial activity against *Staphylococcus aureus* and *Pseudomonas aeruginosa* and good stability towards the renal enzyme dehydropeptidase I (DHP-I).

SOURCE – Fujisawa.

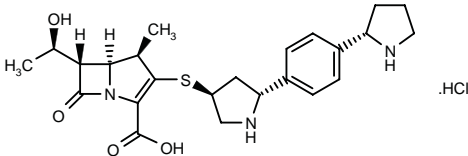
REFERENCES

1. Murata, M. et al. (Fujisawa Pharmaceutical Co., Ltd.) *1-Azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid cpds.* EP 0394991, JP 1990300187, US 5102877.

2. Hattori, K. et al. *Synthesis and antibacterial evaluation of novel 2-[N-imidoyl-pyrrolidinyl] carbapenems.* Bioorg Med Chem Lett 2002, 12(3): 383.

319960

(1*R*,5*S*,6*S*)-6-[1(*R*)-Hydroxyethyl]-1-methyl-2-[5(*R*)-[4-[(2*S*)-pyrrolidinyl]phenyl]pyrrolidin-3(*S*)-ylsulfany]-1-carba-2-penem-3-carboxylic acid hydrochloride



C24 H31 N3 O4 S . HCl; Mol wt: 494.0528

ACTION – Carbapenem antibacterial agent giving MIC values of 0.78 and 1.56 µg/ml, respectively, against *Staphylococcus aureus* BB5939 and *Staphylococcus epidermidis* BB5974 strains.

SOURCE – Banyu.

REFERENCES

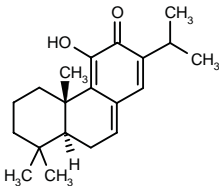
1. Imamura, H. et al. (Banyu Pharmaceutical Co., Ltd.) *Novel carbapenem derivs.* JP 2002088083.

ANTIBACTERIAL DRUGS

318823

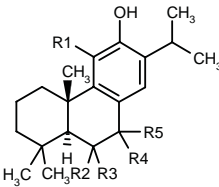
11-Hydroxyabieta-7,9(11),13-trien-12-one

(4*bS*,8*aS*)-4-Hydroxy-2-isopropyl-4*b*,8,8-trimethyl-3,4*b*,5,6,7,8,8*a*,9-octahydrophenanthren-3-one

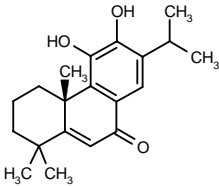


C20 H28 O2; Mol wt: 300.4392

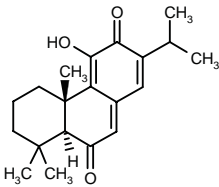
ACTION – Antibacterial agent particularly useful for the treatment of infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA) and/or vancomycin-resistant enterococci (VRE); compound gave MIC values of 0.5 and 1 µg/ml against a panel of MRSA and VRE strains, respectively. Other exemplified compounds are:



Compound	R1	R2	R3	R4	R5	Formula
318824	OH	H	H	-O-		C ₂₀ H ₂₈ O ₃
318826	H	-O-		H	H	C ₂₀ H ₂₈ O ₂
318827	H	H	beta-OH	H	H	C ₂₀ H ₃₀ O ₂



318825: C20 H26 O3



318828: C20 H26 O3

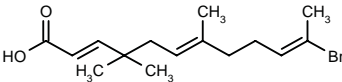
SOURCE – Japan Science and Technology.

REFERENCES

1. Tada, Z. and Arakawa, Y. (Japan Science and Technology Corp.) *Antibacterial cpds. to VRE and/or MRSA.* JP 2002080419.

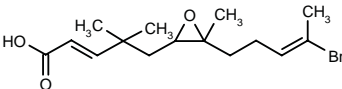
318841

11-Bromo-4,4,7-trimethyldodeca-2,6,10-trienoic acid



C15 H23 Br O2; Mol wt: 315.2487

ACTION – Bacterial signal transduction inhibitor that acts through inhibition of the histidine kinase activity of the sensor YycG (IC₅₀ = 750 µM). Compound demonstrated activity *in vitro* against a panel of bacteria including drug-resistant strains. Another exemplified compound is:



318846: C15 H23 Br O3

SOURCE – Kinki University, Osaka (JP).

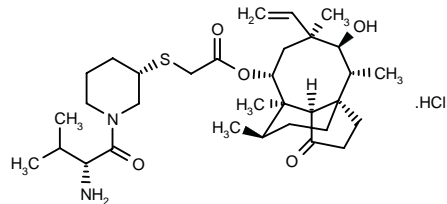
REFERENCES

1. Utsumi, R. et al. (Kinki University) *Bacterial signal transduction inhibitors.* JP 2002069034.

319335

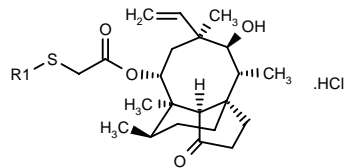
2-[1-(D-Valyl)piperidin-3(S)-ylsulfanyl]acetic acid (3a*S*,4*R*,5*S*,6*S*,8*R*,9*R*,9a*R*,10*R*)-5-hydroxy-4,6,9,10-tetramethyl-1-oxo-6-vinylperhydro-3a,9-propanocyclopentacycloocten-8-yl ester hydrochloride

14-*O*-[2-[1-(D-Valyl)piperidin-3(S)-ylsulfanyl]acetyl]mutilin hydrochloride



C32 H52 N2 O5 S . HCl; Mol wt: 613.2987

ACTION – Mutilin antibacterial agent reported to be active against Gram-positive bacteria, as well as against *Mycoplasma*, *Chlamydia*, *Bacteroides fragilis* and multidrug-resistant strains. Other exemplified 14-*O*-acyl-mutilin derivatives are:



Compound	R1	Formula
319336	1-(H-D-Val)-4-Pip	C ₃₂ H ₅₂ N ₂ O ₅ S.HCl
319337	1-(H-L-Val)-3(S)-Pip-CH2	C ₃₃ H ₅₄ N ₂ O ₅ S.HCl
319338	1-(H-D-Val)-2(R)-pyrrolidinyl-CH2	C ₃₂ H ₅₂ N ₂ O ₅ S.HCl
319339	1-(H-D-Val)-3-pyrrolidinyl-CH2	C ₃₂ H ₅₂ N ₂ O ₅ S.HCl
319340	1-(H-D-His)-3-pyrrolidinyl-CH2	C ₃₃ H ₅₀ N ₄ O ₅ S.HCl

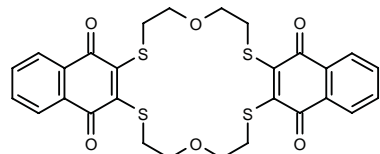
SOURCE – Biochemie.

REFERENCES

1. Ascher, G. et al. (Biochemie GmbH) *Antibacterial mutilins*. WO 0222580.

319346

7,8,10,11,20,21,23,24-Octahydrodinaphtho[2,3-*e*:2',3'-*n*]-[1,10,4,7,13,16]dioxatetrathiacyclooctadecin-5,13,18,26-tetrone



C28 H24 O6 S4; Mol wt: 584.7556

ACTION – Synthetic naphthoquinone thiol-crown ether with potent antibacterial activity, comparable to gentamicin, against methicillin-resistant *Staphylococcus aureus* (MIC = 2.68 and 0.78 µM, respectively). Compound also exhibited weak antifungal activity against *Candida albicans* and *Trichophyton mentagrophytes* (MIC = 10.7 and 5.34 µM, respectively), as well as moderate cytotoxic activity against several human carcinoma cell lines.

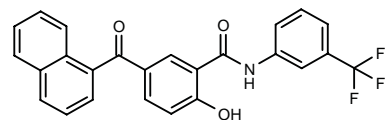
SOURCE – Taipei Medical College, Taipei (TW).

REFERENCES

1. Huang, S.-T. et al. *Efficient synthesis of “redox-switched” naphthoquinone thiol-crown ethers and their biological activity evaluation*. Bioorg Med Chem 2002, 10(6): 1947.

319675

2-Hydroxy-5-(naphthalen-1-ylcarbonyl)-*N*-[3-(trifluoromethyl)phenyl]benzamide



C25 H16 F3 N O3; Mol wt: 435.3994

ACTION – A representative compound from a series of naphthylsalicylanilides with antibacterial and antiinflammatory activity. Compound demonstrated *in vitro* activity against a broad panel of Gram-positive and Gram-negative bacterial strains.

SOURCE – State University of New York, Buffalo, NY (US).

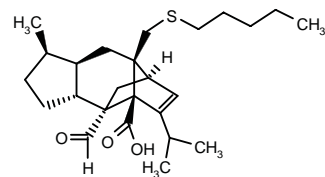
REFERENCES

1. Coburn, R.A. et al. (State University of New York, Buffalo) *Naphthylsalicylanilides as antimicrobial and antiinflammatory agents*. WO 0228819.

ANTIFUNGAL AGENTS

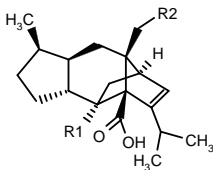
319320

(1*R*,3a*S*,4*S*,4a*R*,7*R*,7a*R*,8a*S*)-4-Formyl-3-isopropyl-7-methyl-8a-(pentylsulfanylmethyl)-1,3a,4,4a,5,6,7,7a,8,8a-decahydro-1,4-methano-*s*-indacene-3a-carboxylic acid



C25 H38 O3 S; Mol wt: 418.6382

ACTION – Antifungal sordaricin analogue particularly useful for the treatment of infections caused by *Candida albicans* and *Candida glabrata*. Other specifically claimed compounds are:



Compound	R1	R2	Formula
319321	CHO	i-BuCH2S	C ₂₅ H ₃₈ O ₃ S
319324	CHO	SC6H13	C ₂₆ H ₄₀ O ₃ S
319325	CHO	i-BuCH2SO	C ₂₅ H ₃₈ O ₄ S
319326	CHO	i-BuCH2SO2	C ₂₅ H ₃₈ O ₅ S
319327	CH=NN(Me)2	i-BuCH2S	C ₂₇ H ₄₄ N ₂ O ₂ S
319328	CHO	2-Me-5-isoxazolidinyl-CH2S	C ₂₅ H ₃₇ NO ₄ S
319329	CHO	3-Me-4,5-dihydroisoxazol-5-yl-CH2S	C ₂₅ H ₃₅ NO ₄ S

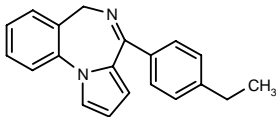
SOURCE – Bristol-Myers Squibb.

REFERENCES

1. Serrano-Wu, M. et al. (Bristol-Myers Squibb Co.) *Novel thio derivs. of sordarin as antifungal agents*. WO 0222567.

319536

4-(4-Ethylphenyl)-6*H*-pyrrolo[1,2-*a*][1,4]benzodiazepine



C20 H18 N2; Mol wt: 286.3762

ACTION – Antifungal agent, a representative compound from a series of pyrrolo[1,2-*a*][1,4]benzodiazepine derivatives, with *in vitro* activity against *Sporothrix schenckii* (MIC = 10 μM), *Microsporum canis* (MIC = 0.32 μM), *Trichophyton rubrum* (MIC = 0.03 μM), *Trichophyton mentagrophytes* (MIC = 0.32 μM), *Candida parapsilosis* (MIC = 3.2 μM) and *Aspergillus fumigatus* (MIC = 1 μM).

SOURCE – Janssen.

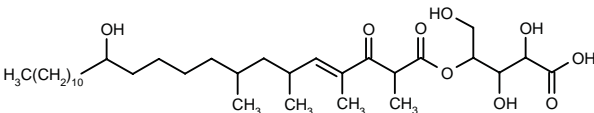
REFERENCES

1. Gilkerson, T. et al. (Janssen Pharmaceutica NV) *Antifungal 4-substd. 5,6-dihyro-4H-pyrrolo[1,2-*a*][1,4]benzodiazepines*. WO 0234752.

F-15949-1

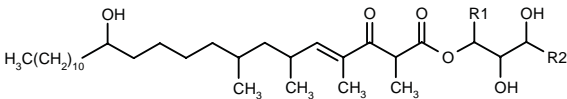
319371

2,3,5-Trihydroxy-4-(13-hydroxy-2,4,6,8-tetramethyl-3-oxotetracos-4-enoyloxy)pentanoic acid



C33 H60 O9; Mol wt: 600.8280

ACTION – Antifungal agent isolated from cultures of *Haplographium heliocephalum* SANK 26899 (FERM BP-7243), displaying MIC values of 16 μg/ml against *Candida albicans* ATCC24433 and ATCC90030 strains. Other exemplified compounds from the same source are:



Compound	R1	R2	Formula
F-15949-2 [319372]	H	CH(OH)CO2H	C ₃₃ H ₆₀ O ₉
F-15949-4 [319373]	CH2OH	CO2Me	C ₃₄ H ₆₂ O ₉

SOURCE – Sankyo.

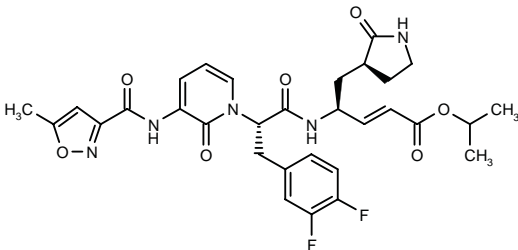
REFERENCES

1. Ohnuki, T. et al. (Sankyo Co., Ltd.) *Novel cpd. F-15949*. WO 0220816.

ANTIVIRAL DRUGS

317882

4(*S*)-[3-(3,4-Difluorophenyl)-2(*S*)-[3-(5-methylisoxazol-3-ylcarboxamido)-2-oxo-1,2-dihydropyridin-1-yl]-propionamido]-5-[2-oxopyrrolidin-3(*S*)-yl]-2(*E*)-pentenoic acid isopropyl ester



C31 H33 F2 N5 O7; Mol wt: 625.6257

ACTION – Orally active inhibitor of human rhinovirus 3C protease with excellent activity against various serotypes of human rhinovirus (EC₅₀ = 3 nM) and no cytotoxicity at > 10 μM. It exhibited good stability in human liver microsomes and a prolonged half-life (9.7 h) in human plasma. Pharmacokinetic studies in dogs showed that high (exceeding the average *in vitro* EC₅₀ for antirhinoviral activity) and sustained (> 8 h) plasma levels were achieved at the dose of 30 mg/kg p.o.; the oral bioavailability was 48% in this species. Potentially useful for the treatment of the common cold.

SOURCE – Agouron (Pfizer).

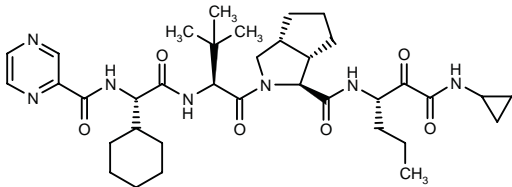
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1. Dragovich, P.S. et al. (Agouron Pharmaceuticals, Inc.) *Antipicornaviral cpds. and compsns., their pharmaceutical uses, and material for their synthesis*. WO 0140189.

2. Dragovich, P.S. et al. *Structure-based design, synthesis, and biological evaluation of irreversible human rhinovirus 3C protease inhibitors: 6. Structure-activity studies of orally bioavailable, 2-pyridone-containing peptidomimetics*. J Med Chem 2002, 45(8): 1607.

318445

(1*S*,3*aR*,6*aS*)-2-[*N*-(Pyrazin-2-ylcarbonyl)-*L*-cyclohexylglycyl-3-methyl-*L*-valyl]-*N*-[1(*S*)-[2-(cyclopropylamino)-oxalyl]butyl]perhydrocyclopenta[*c*]pyrrole-1-carboxamide



C36 H53 N7 O6; Mol wt: 679.8577

ACTION – Peptidomimetic inhibitor of hepatitis C virus (HCV) NS3 protease, potentially useful for the prevention and treatment of HCV infection. The compound demonstrated NS3-inhibitory activity *in vitro*, and a synergistic effect was observed when this compound was combined with interferon alfa-2b.

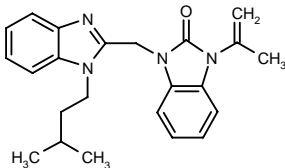
SOURCE – Lilly.

REFERENCES

1. Babine, R.E. et al. (Eli Lilly and Company) *Peptidomimetic protease inhibitors*. WO 0218369.

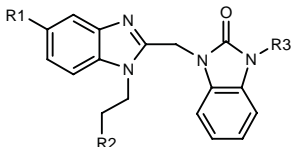
318879

1-[1-(3-Methylbutyl)-1*H*-benzimidazol-2-ylmethyl]-3-(1-methylvinyl)-2,3-dihydro-1*H*-benzimidazol-2-one



C23 H26 N4 O; Mol wt: 374.4854

ACTION – Antiviral agent with potential for use in the treatment of respiratory syncytial virus (RSV) infection. Other exemplified 2,3-dihydro-1*H*-benzimidazol-2-one derivatives include the following:



Compound	R1	R2	R3	Formula
318880	H	i-Pr	4-(BrCH2)-PhCH2	C ₂₈ H ₂₉ BrN ₄ O
318881	H	1-Me-5-tetrazolyl	C(Me)=CH2	C ₂₂ H ₂₂ N ₈ O
318882	H	N(Me)2	i-Pr	C ₂₂ H ₂₇ N ₅ O
318883	H	5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl	i-Pr	C ₂₂ H ₂₂ N ₆ O ₃
318884	H	N(Me)2	4-NH2-PhCH2	C ₂₆ H ₂₈ N ₆ O
318885	H	1-tetrazolyl	H	C ₁₈ H ₁₆ N ₈ O
318886	H	OH	CH2CO2Et	C ₂₁ H ₂₂ N ₄ O ₄
318887	Ac	i-Pr	Me	C ₂₃ H ₂₆ N ₄ O ₂

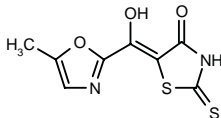
SOURCE – Bristol-Myers Squibb.

REFERENCES

1. Yu, K.-L. et al. (Bristol-Myers Squibb Co.) *Benzimidazole antiviral agents*. WO 0226228.

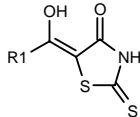
319416

5-[1-Hydroxy-1-(5-methyloxazol-2-yl)methylene]-2-thioxo-thiazolidin-4-one



C8 H6 N2 O3 S2; Mol wt: 242.2784

ACTION – Antiviral agent able to inhibit hepatitis C virus (HCV) RNA-dependent RNA synthase and therefore potentially useful for the treatment of HCV infection. Compound gave IC₅₀ values of 0.25 and 2.5 µg/ml, respectively, against HCV RNA-dependent RNA synthase (RdRp) and bovine viral diarrhea virus RdRp. Other exemplified compounds are:



Compound	R1	Formula
319417	2-furyl	C ₈ H ₅ NO ₃ S ₂
319420	5-Me-2-furyl	C ₉ H ₇ NO ₃ S ₂
319421	4-Me-5-isoxazolyl	C ₈ H ₆ N ₂ O ₃ S ₂
319422	3-isoxazolyl	C ₇ H ₄ N ₂ O ₃ S ₂
319423	5-isoxazolyl	C ₇ H ₄ N ₂ O ₃ S ₂
319424	2H-tetrazol-5-yl	C ₅ H ₄ N ₅ O ₂ S ₂
319425	1,2,4-triazol-3-yl	C ₆ H ₄ N ₄ O ₂ S ₂
319426	2-pyrimidinyl	C ₈ H ₅ N ₃ O ₂ S ₂
319428	2-pyrazinyl	C ₈ H ₅ N ₃ O ₂ S ₂
319429	2-Pyr	C ₉ H ₆ N ₂ O ₂ S ₂
319431	5-Me-1,3,4-oxadiazol-2-yl	C ₇ H ₅ N ₃ O ₃ S ₂

SOURCE – Shionogi.

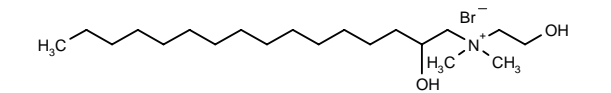
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AIDS MEDICINES

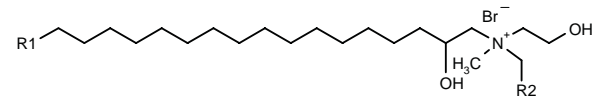
317716^{1,2}

2-Hydroxy-*N*-(2-hydroxyethyl)-*N,N*-dimethyl-1-hexadecanaminium bromide



C20 H44 Br N O2; Mol wt: 410.4766

ACTION – Trihydroxylated cationic surfactant with spermicidal and anti-HIV activity, potentially useful for the prevention of HIV infection. Other related compounds are:



Compound	R1	R2	Formula
317717 ²	H	H	C ₂₁ H ₄₆ BrNO ₂
317718 ²	Me	H	C ₂₂ H ₄₈ BrNO ₂
317719 ²	H	CH2OH	C ₂₂ H ₄₈ BrNO ₃

SOURCES – Eastern Virginia Medical School, Norfolk, VA (US); Virginia Tech, Blacksburg, VA (US).

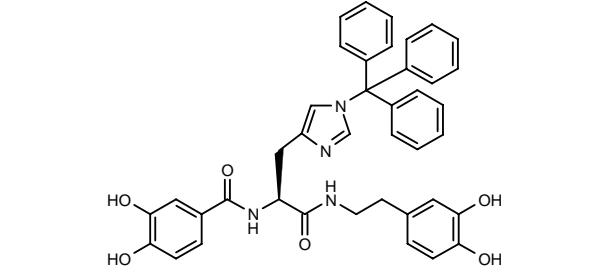
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1. Rutzen, H. (Henkel KgA) *Process for the preparation of quaternary ammonium cpds.* DE 3136628, EP 0075066, JP 1983046043, US 4480126.

2. Wong, Y.L. et al. *Spermicidal, anti-HIV, and micellar properties of di- and trihydroxylated cationic surfactants.* Tetrahedron 2002, 58(1): 45.

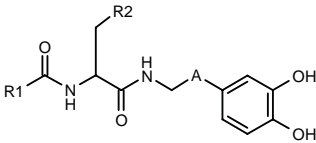
318692

*N*²-(3,4-Dihydroxybenzoyl)-*N*¹-[2-(3,4-dihydroxyphenyl)-ethyl]-*N*^τ-trityl-L-histidinamide



C40 H36 N4 O6; Mol wt: 668.7464

ACTION – Antiviral agent with HIV integrase-inhibitory activity (IC₅₀ = 65 nM). Other exemplified aromatic compounds are:



Compound	R1	R2	A	Isomer	Formula
318694	3,4-(OH)2-Ph	1-[(Ph)3C]-4-imidazolyl	-CH2-	D	C ₄₀ H ₃₆ N ₄ O ₆
318699	3,4-(OH)2-Ph	1-[2,4-(NO2)2-Ph]-4-imidazolyl	-CH2-	L	C ₂₇ H ₂₄ N ₆ O ₁₀
318700	3,4-(OH)2-Ph	1-[2,4-(NO2)2-Ph]-4-imidazolyl	bond	L	C ₂₆ H ₂₂ N ₆ O ₁₀
318703	3,4-(OH)2-PhCH=CH	4-Me-PhC(Ph)2-NHCOCH2	bond	L	C ₄₁ H ₃₆ N ₃ O ₇
318704	3,4,5-(OH)3-Ph	t-BuO	-CH2-	L	C ₂₂ H ₂₈ N ₂ O ₈

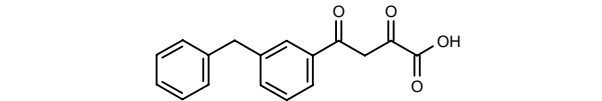
SOURCE – Pharmacor.

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1. N'Zemba, B.M. et al. (Pharmacor Inc.) *Aromatic derivs. with HIV integrase inhibitory properties.* WO 0226697.

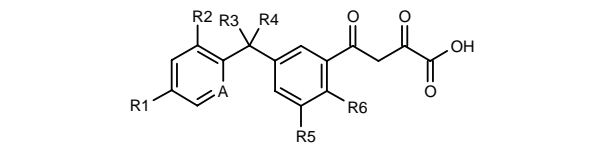
319622

4-(3-Benzylphenyl)-2,4-dioxobutyrlic acid



C17 H14 O4; Mol wt: 282.2936

ACTION – Antiviral agent that acts by inhibiting HIV integrase, and is thus potentially useful for the treatment of HIV infection. Other specifically claimed 2,4-dioxobutyrlic acid derivatives include the following:



Compound	R1	R2	R3	R4	R5	R6	A	Formula
319623	H	H	H	H	2-pyrazinyl	H	CH	C ₂₁ H ₁₆ N ₂ O ₄
319624	F	F	H	H	H	H	CH	C ₁₇ H ₁₂ F ₂ O ₄
319625	H	H	H	H	H	Me2NCH2CH2O	CH	C ₂₁ H ₂₃ NO ₅
319626	H	H	H	H	OMe	OMe	CH	C ₁₉ H ₁₈ O ₆
319627	H	Cl	H	H	H	H	N	C ₁₆ H ₁₂ ClNO ₄
319629	H	H	H	H	OMe	Me2N(CH2)3O	CH	C ₂₃ H ₂₇ NO ₆
319630	H	H	F	F	H	H	CH	C ₁₇ H ₁₂ F ₂ O ₄
319631	H	H	H	H	2-Pyr-NHCH2	iPr-O	CH	C ₂₆ H ₂₆ N ₂ O ₅

SOURCES – Merck & Co.; Tularik.

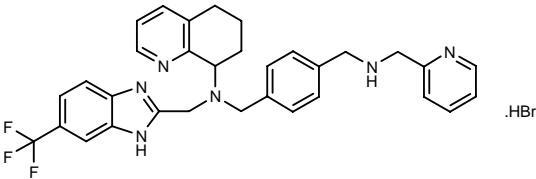
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1. Young, S.D. et al. (Merck & Co., Inc.;Tularik Inc.) *HIV integrase inhibitors.* US 6380249.

AMD-8936

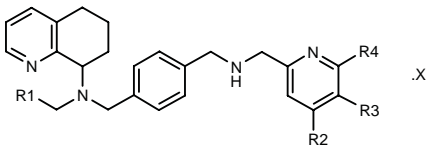
319435

N-[4-(Pyridin-2-ylmethylaminomethyl)benzyl]-*N*-[6-(trifluoromethyl)-1*H*-benzimidazol-2-ylmethyl]-5,6,7,8-tetrahydroquinolin-8-amine hydrobromide



C32 H31 F3 N6 . HBr ; Mol wt: 637.5448

ACTION – A modulator of chemokine receptors, particularly CXCR4 and CCR5 receptors, potentially useful for the treatment of HIV infection. It was shown to inhibit SDF-1-induced Ca flux in SIP-T1 cells and prevented HIV-1 replication in MT-4 cells and in PHA-stimulated peripheral blood mononuclear cells. Other exemplified compounds are:



Compound	R1	R2	R3	R4	X	Formula
AMD-8927 [319436]	5,6-(Me)2- -2-benzimidazolyl	H	H	H	HBr	C ₃₃ H ₃₆ N ₆ .HBr
AMD-9336 [319437]	4-MeO- -2-benzimidazolyl	H	H	H	HBr	C ₃₂ H ₃₄ N ₆ O.HBr
AMD-8931 [319438]	5-Ph-2-imidazolyl	H	H	H		C ₃₃ H ₃₄ N ₆
AMD-8999 [319439]	5-(3-MeO-Ph)- -2-imidazolyl	H	H	H		C ₃₄ H ₃₆ N ₆ O
AMD-9398 [319440]	2-benzimidazolyl	H	Bu	H	HBr	C ₃₅ H ₄₀ N ₆ .HBr
AMD-9437 [319441]	2-benzimidazolyl	Me	H	Me	HBr	C ₃₃ H ₃₆ N ₆ .HBr

SOURCE – AnorMED.

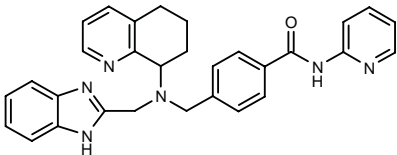
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1. Bridger, G. et al. (AnorMED Inc.) *Chemokine receptor binding heterocyclic cpds.* WO 0222600.

AMD-9370

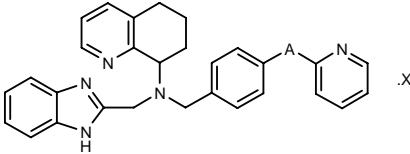
319419

4-[*N*-(1*H*-Benzimidazol-2-ylmethyl)-*N*-(5,6,7,8-tetrahydroquinolin-8-yl)aminomethyl]-*N*-(2-pyridyl)benzamide



C30 H28 N6 O; Mol wt: 488.5922

ACTION – A modulator of chemokine receptors, particularly CXCR4 and CCR5 receptors, potentially useful for the treatment of HIV infection. It was shown to inhibit SDF-1-induced Ca flux in SIP-T1 cells and it prevented HIV-1 replication in MT-4 cells and in PHA-stimulated peripheral blood mononuclear cells. Other exemplified compounds are:



Compound	A	X	Formula
AMD-9369 [319427]	-CONHCH2-	HBr	C ₃₁ H ₃₀ N ₆ O.HBr
AMD-9371 [319430]	-SO2NHCH2-		C ₃₀ H ₃₀ N ₆ O ₂ S
AMD-9401 [319432]	-CH2NHCO-		C ₃₁ H ₃₀ N ₆ O
AMD-9413 [319433]	-NHCO-		C ₃₀ H ₂₈ N ₆ O
AMD-9429 [319434]	-CH2NHOSO2-	HBr	C ₃₀ H ₃₀ N ₆ O ₂ S.HBr

SOURCE – AnorMED.

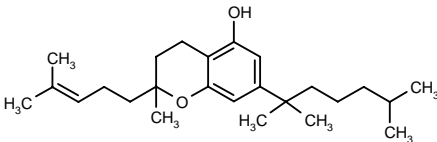
REFERENCES

1. Bridger, G. et al. (AnorMED Inc.) *Chemokine receptor binding heterocyclic cpds.* WO 022599.

IG-08

318905

2-Methyl-2-(4-methyl-3-pentenyl)-7-(1,1,5-trimethylhexyl)-3,4-dihydro-2*H*-1-benzopyran-5-ol



C25 H40 O2; Mol wt: 372.5890

ACTION – A representative compound from a series of cannabichromene derivatives, useful for the treatment of viral infections and more particularly HIV infections. IG-08 demonstrated anti-HIV activity in a panel of cell-based assays.

SOURCE – Immugen.

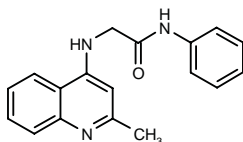
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TREATMENT OF PROTOZOAL DISEASES

319276

2-(2-Methylquinolin-4-ylamino)-N-phenylacetamide



C₁₈ H₁₇ N₃ O; Mol wt: 291.3523

ACTION – Antileishmanial agent shown to inhibit the growth of *Leishmania donovani* in a concentration-dependent manner (1-5 µg/ml), with 95% inhibition at 5 µg/ml after 7 days of culture. It was more active than the reference sodium antimony gluconate in reducing the parasite load both in the spleen and liver of *L. donovani*-infected hamsters, but was devoid of liver toxicity.

SOURCE – Indian Institute of Chemical Biology, Calcutta (IN).

REFERENCES

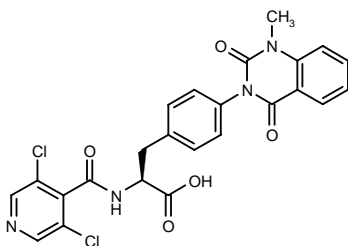
1. Sahu, N.P. et al. *Synthesis of a novel quinoline derivative, 2-(2-methylquinolin-4-ylamino)-N-phenylacetamide - A potential antileishmanial agent.* Bioorg Med Chem 2002, 10(6): 1687.

TREATMENT OF MUSCULOSKELETAL AND CONNECTIVE TISSUE DISEASES

ANTIARTHRITIC DRUGS

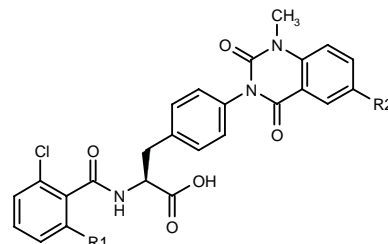
318436

N-(3,5-Dichloropyridin-4-ylcarbonyl)-4-(1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-3-yl)-L-phenylalanine



C₂₄ H₁₈ Cl₂ N₄ O₅; Mol wt: 513.3352

ACTION – Cell adhesion inhibitor that inhibited the binding of VCAM-1 to $\alpha_4\beta_7$ - and $\alpha_4\beta_1$ -expressing Jurkat cells with IC₅₀ values of 0.5 and 6 nM, respectively. Potentially useful for the treatment of inflammatory disorders such as rheumatoid arthritis, inflammatory bowel disease, systemic lupus erythematosus, multiple sclerosis, Sjögren's syndrome, asthma, psoriasis, allergy, diabetes, cardiovascular diseases, arteriosclerosis, restenosis, cancer and transplant rejection. Other exemplified phenylalanine derivatives are:



Compound	R1	R2	Formula
318437	Cl	NHCOCH ₂ OMe	C ₂₈ H ₂₄ Cl ₂ N ₄ O ₇
318438	Br	H	C ₂₅ H ₁₉ BrClN ₃ O ₅

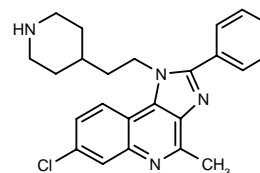
SOURCE – Ajinomoto.

REFERENCES

1. Makino, S. et al. (Ajinomoto Co., Inc.) *Novel phenylalanine derivs.* WO 0216329.

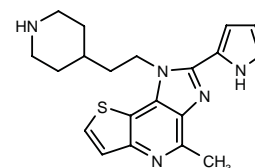
318443

7-Chloro-4-methyl-2-phenyl-1-[2-(4-piperidiny)ethyl]-1H-imidazo[4,5-c]quinoline



C₂₄ H₂₅ Cl N₄; Mol wt: 404.9425

ACTION – Cytokine production inhibitor that was shown to concentration-dependently inhibit TNF- α and IL-1 β production in human peripheral blood mononuclear cells. Potentially useful for the treatment of cytokine (TNF or IL-1)-mediated disorders including chronic inflammatory diseases, allergic rhinitis, atopic dermatitis, asthma, sepsis, autoimmune diseases, multiple sclerosis, sarcoidosis, systemic lupus erythematosus, psoriasis, chronic hepatitis, pulmonary fibrosis, diabetes, cancer and cachexia. Another exemplified imidazopyridine derivative is:

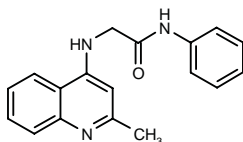


318444: C₂₀ H₂₃ N₅ S

TREATMENT OF PROTOZOAL DISEASES

319276

2-(2-Methylquinolin-4-ylamino)-N-phenylacetamide



C₁₈ H₁₇ N₃ O; Mol wt: 291.3523

ACTION – Antileishmanial agent shown to inhibit the growth of *Leishmania donovani* in a concentration-dependent manner (1-5 µg/ml), with 95% inhibition at 5 µg/ml after 7 days of culture. It was more active than the reference sodium antimony gluconate in reducing the parasite load both in the spleen and liver of *L. donovani*-infected hamsters, but was devoid of liver toxicity.

SOURCE – Indian Institute of Chemical Biology, Calcutta (IN).

REFERENCES

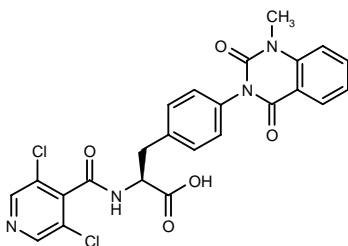
1. Sahu, N.P. et al. *Synthesis of a novel quinoline derivative, 2-(2-methylquinolin-4-ylamino)-N-phenylacetamide - A potential antileishmanial agent.* Bioorg Med Chem 2002, 10(6): 1687.

TREATMENT OF MUSCULOSKELETAL AND CONNECTIVE TISSUE DISEASES

ANTIARTHRITIC DRUGS

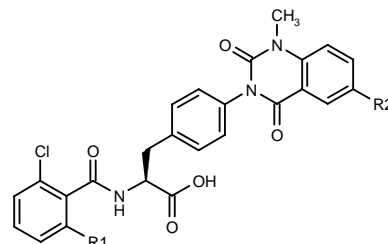
318436

N-(3,5-Dichloropyridin-4-ylcarbonyl)-4-(1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-3-yl)-L-phenylalanine



C₂₄ H₁₈ Cl₂ N₄ O₅; Mol wt: 513.3352

ACTION – Cell adhesion inhibitor that inhibited the binding of VCAM-1 to $\alpha_4\beta_7$ - and $\alpha_4\beta_1$ -expressing Jurkat cells with IC₅₀ values of 0.5 and 6 nM, respectively. Potentially useful for the treatment of inflammatory disorders such as rheumatoid arthritis, inflammatory bowel disease, systemic lupus erythematosus, multiple sclerosis, Sjögren's syndrome, asthma, psoriasis, allergy, diabetes, cardiovascular diseases, arteriosclerosis, restenosis, cancer and transplant rejection. Other exemplified phenylalanine derivatives are:



Compound	R1	R2	Formula
318437	Cl	NHCOCH ₂ OMe	C ₂₈ H ₂₄ Cl ₂ N ₄ O ₇
318438	Br	H	C ₂₅ H ₁₉ BrClN ₃ O ₅

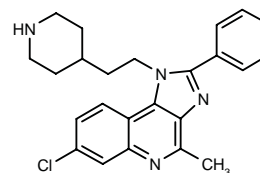
SOURCE – Ajinomoto.

REFERENCES

1. Makino, S. et al. (Ajinomoto Co., Inc.) *Novel phenylalanine derivs.* WO 0216329.

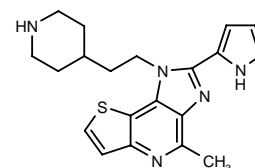
318443

7-Chloro-4-methyl-2-phenyl-1-[2-(4-piperidiny)ethyl]-1H-imidazo[4,5-c]quinoline



C₂₄ H₂₅ Cl N₄; Mol wt: 404.9425

ACTION – Cytokine production inhibitor that was shown to concentration-dependently inhibit TNF- α and IL-1 β production in human peripheral blood mononuclear cells. Potentially useful for the treatment of cytokine (TNF or IL-1)-mediated disorders including chronic inflammatory diseases, allergic rhinitis, atopic dermatitis, asthma, sepsis, autoimmune diseases, multiple sclerosis, sarcoidosis, systemic lupus erythematosus, psoriasis, chronic hepatitis, pulmonary fibrosis, diabetes, cancer and cachexia. Another exemplified imidazopyridine derivative is:



318444: C₂₀ H₂₃ N₅ S

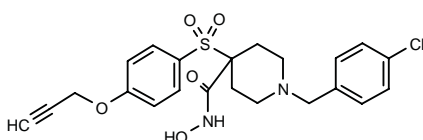
SOURCE – Hokuriku.

REFERENCES

1. Kato, H. et al. (Hokuriku Seiyaku Co., Ltd.) *1H-Imidazopyridine derivs.* WO 0216370.

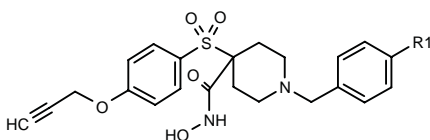
318745

1-(4-Chlorobenzyl)-4-[4-(2-propynyloxy)phenylsulfonyl]-piperidine-4-carboxylic acid



C22 H23 Cl N2 O5 S; Mol wt: 462.9517

ACTION – An inhibitor of TNF- α -converting enzyme (TACE) and other matrix metalloproteinases (MMPs), giving IC₅₀ values of 127, 91, 16 and 4.7 nM, respectively, against TACE, MMP-1 (interstitial collagenase), MMP-9 (gelatinase B) and MMP-13 (collagenase 3). Potentially useful for the treatment of rheumatoid arthritis, transplant rejection, cachexia, inflammation, fever, insulin resistance, septic shock, congestive heart failure, CNS inflammatory diseases, inflammatory bowel disease and HIV infection. Other exemplified alkynyl-containing carboxylic acids are:



Compound	R1	Formula
318746	Br	C ₂₂ H ₂₃ BrN ₂ O ₅ S
318747	OMe	C ₂₃ H ₂₆ N ₂ O ₆ S

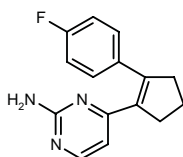
SOURCE – Wyeth.

REFERENCES

1. Levin, J.I. et al. (American Cyanamid Company) *Alkynyl containing hydroxamic acid cpds. as matrix metalloproteinase/TACE inhibitors.* US 6358980.

318802

4-[2-(4-Fluorophenyl)-1-cyclopenten-1-yl]pyrimidin-2-amine



C15 H14 F N3; Mol wt: 255.2946

ACTION – A specifically claimed compound within a series of cyclopentenyl derivatives with the ability to inhibit the production of the proinflammatory cytokines IL-1, IL-8 and TNF through inhibition of CSBP/p38 kinase (IC₅₀ < 50 μ M). Potentially useful for the treatment of arthritis, Reiter's syndrome, gout, acute synovitis, rheumatoid spondylitis, sepsis, Alzheimer's disease, stroke, neuro-trauma, asthma, adult respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, osteoporosis, restenosis, cardiac and renal reperfusion injury, thrombosis, glomerulonephritis, diabetes, transplant rejection, inflammatory bowel disease, Crohn's disease, ulcerative colitis, multiple sclerosis, muscle degeneration, diabetic retinopathy, macular degeneration, eczema, contact dermatitis, psoriasis, sunburn and conjunctivitis.

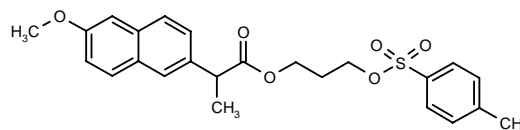
SOURCE – GlaxoSmithKline.

REFERENCES

1. Adams, J.L. and Garigipati, R. (GlaxoSmithKline Inc.) *Cycloalkenyl subst. cpds.* US 6362193, WO 9917776.

318829

2-(6-Methoxynaphthalen-2-yl)propionic acid 3-(4-methylphenylsulfonyloxy)propyl ester



C24 H26 O6 S; Mol wt: 442.5294

ACTION – Nonsteroidal antiinflammatory drug (NSAID), a prodrug of naproxen modified with a sulfur-containing functional group, reported to be associated with a lower incidence of side effects compared to unmodified NSAIDs. The prodrug displayed *in vivo* activity comparable to the parent drug following oral administration in a rat model of carrageenan-induced acute inflammation. Pharmacokinetic studies in rats demonstrated the release of naproxen following oral administration of title compound. Potentially useful for the treatment of septic shock, cerebral ischemia, ulcers, inflammatory bowel disease, diabetes, arthritis, asthma, Alzheimer's disease, Parkinson's disease, multiple sclerosis, cirrhosis, transplant rejection, encephalomyelitis, pancreatitis, peritonitis, vasculitis, inflammation, infection, stroke, cancer, gastritis, adult respiratory distress syndrome, cachexia, autoimmune disorders, psoriasis, heart failure, atherosclerosis, systemic lupus erythematosus, AIDS, pain, etc.

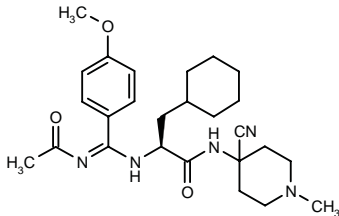
SOURCE – Medinox.

REFERENCES

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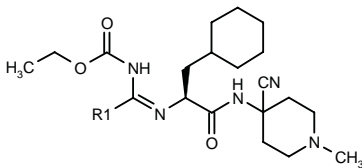
319063

2(S)-[1-(Acetylimino)-1-(4-methoxyphenyl)methylamino]-N-(4-cyano-1-methylpiperidin-4-yl)-3-cyclohexylpropionamide

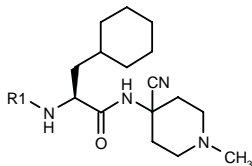


C26 H40 N4 O3; Mol wt: 456.6270

ACTION – An inhibitor of cathepsins S, K, F, L and B, considered to have potential in the treatment of autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, Crohn’s disease, ulcerative colitis, multiple sclerosis, Guillain-Barré syndrome, psoriasis, Graves’ disease, myasthenia gravis, scleroderma, glomerulonephritis, dermatitis, endometriosis and type 1 diabetes. Other exemplified compounds are:



Compound	R1	Formula
319064	4-morpholinyl	C ₂₄ H ₄₃ N ₅ O ₄
319068	hexahydro-1-azepinyl	C ₂₆ H ₄₇ N ₅ O ₃
319069	4-(1-Pip)-1-Pip	C ₃₀ H ₅₄ N ₆ O ₃
319071	3,3,5-(Me)3-6-azabicyclo[3.2.1]oct-6-yl	C ₃₀ H ₅₃ N ₅ O ₃



Compound	R1	Formula
319065	1,1-dioxo-3-benzisothiazolyl	C ₂₃ H ₃₄ N ₄ O ₃ S
319066	1-oxo-3-isoidolyl	C ₂₄ H ₃₄ N ₄ O ₂
319067	4-CF3-2-pyrimidinyl	C ₂₁ H ₃₂ F ₃ N ₅ O

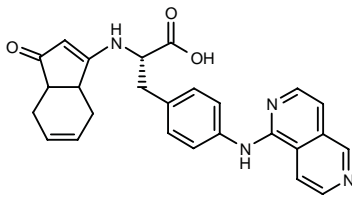
SOURCE – Boehringer Ingelheim.

REFERENCES

1. Bakkali, Y. et al. (Boehringer Ingelheim Pharmaceuticals Inc.) *Spiroheterocyclic nitriles useful as reversible inhibitors of cysteine proteases*. WO 0220485.

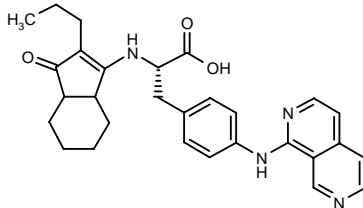
319145

4-(2,6-Naphthyridin-1-ylamino)-N-(1-oxo-3a,4,7,7a-tetrahydro-1H-inden-3-yl)-L-phenylalanine



C26 H24 N4 O3; Mol wt: 440.5006

ACTION – Potent and selective inhibitor of $\alpha_4\beta_1$ and/or $\alpha_4\beta_7$ integrins with good pharmacokinetic properties. Potentially useful for the treatment of inflammatory disorders where extravasation of leukocytes plays a role such as rheumatoid arthritis, vasculitis, polydermatomyositis, multiple sclerosis, transplant rejection, diabetes, inflammatory dermatoses including psoriasis and dermatitis, asthma and inflammatory bowel disease. Another specifically claimed bicyclic enamide derivative is:



319146: C29 H32 N4 O3

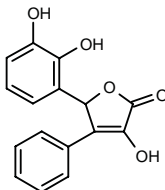
SOURCE – Celltech Group.

REFERENCES

1. Porter, J.R. et al. (Celltech Group plc) *Bicyclic enamide derivs. being integrin inhibitors*. WO 0220522.

319271

5-(2,3-Dihydroxyphenyl)-3-hydroxy-4-phenylfuran-2(5H)-one



C16 H12 O5; Mol wt: 284.2658

ACTION – Antioxidant with reducing activity against the stable radical DPPH (IC₅₀ = 10.3 μ M), superoxide anion-scavenging activity (IC₅₀ = 187 μ M) and lipid peroxidation-inhibitory effect (IC₅₀ = 129 μ M). *In vivo*, compound showed antiinflammatory activity comparable to indomethacin and ketorolac in the phorbol ester-induced ear edema model in mice and carrageenan-induced paw edema model in rats. Potentially useful for the treatment of inflammatory diseases such as rheumatoid arthritis, and for the treatment of heart and brain disorders involving free radicals such as myocardial infarction and stroke.

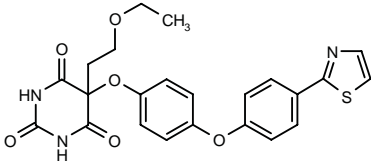
SOURCES – Université d’Auvergne-Clermont-Ferrand, Clermont-Ferrand (FR); Université Blaise Pascal-Clermont-Ferrand II, Clermont-Ferrand (FR).

REFERENCES

1. Weber, V. et al. *Novel 4,5-diaryl-3-hydroxy-2(5H)-furanones as anti-oxidants and anti-inflammatory agents*. Bioorg Med Chem 2002, 10(6): 1647.

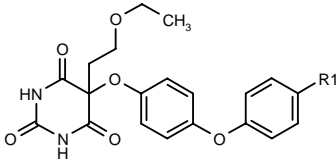
319608

5-(2-Ethoxyethyl)-5-[4-[4-(2-thiazolyl)phenoxy]phenoxy]-perhydropyrimidine-2,4,6-trione



C23 H21 N3 O6 S; Mol wt: 467.4999

ACTION – Matrix metalloproteinase (MMP) inhibitor reported to inhibit MMP-13 (collagenase 3) selectively over other MMP enzymes. Potentially useful for the treatment of connective tissue disorders, inflammation, immune and allergic disorders, infections, respiratory diseases, cardiovascular diseases, eye diseases, metabolic disorders, CNS disorders, liver and kidney diseases, reproductive disorders, gastric and skin disorders and cancer. Other specifically claimed pyrimidine-2,4,6-trione derivatives are:



Compound	R1	Formula
319615	1-Me-5-pyrazolyl	C ₂₄ H ₂₄ N ₄ O ₆
319616	1-Me-3-pyrazolyl	C ₂₄ H ₂₄ N ₄ O ₆
319617	(CH2)4CN	C ₂₅ H ₂₇ N ₃ O ₆
319618	2-Me-4-thiazolyl	C ₂₄ H ₂₃ N ₃ O ₆ S
319619	3-pyrazolyl	C ₂₃ H ₂₂ N ₄ O ₆
319620	5-oxazolyl	C ₂₃ H ₂₁ N ₃ O ₇
319621	4-pyrimidinyl	C ₂₄ H ₂₂ N ₄ O ₆

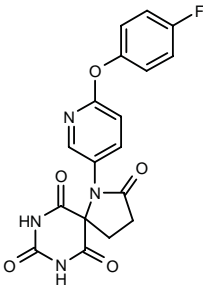
SOURCE – Pfizer.

REFERENCES

1. Noe, M.C. et al. (Pfizer Products Inc.) *Pyrimidine-2,4,6-trione metalloproteinase inhibitors*. WO 0234726.

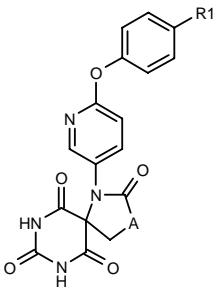
319628

1-[6-(4-Fluorophenoxy)pyridin-3-yl]-1,7,9-triazaspiro[4.5]-decane-2,6,8,10-tetraone



C18 H13 F N4 O5; Mol wt: 384.3217

ACTION – Matrix metalloproteinase (MMP) inhibitor reported to inhibit MMP-13 (collagenase 3) selectively over other MMP enzymes. Potentially useful for the treatment of connective tissue disorders, inflammation, immune and allergic disorders, infections, respiratory diseases, cardiovascular diseases, eye diseases, metabolic disorders, CNS disorders, liver and kidney diseases, reproductive disorders, gastric and skin disorders and cancer. Other specifically claimed spiro-pyrimidine-2,4,6-trione derivatives are:



Compound	R1	A	Formula
319632	F	-(CH2)2-	C ₁₉ H ₁₅ FN ₄ O ₅
319633	CN	-CH2-	C ₁₉ H ₁₃ N ₅ O ₅
319634	1,3,4-oxadiazol-2-yl	-CH2-	C ₂₀ H ₁₄ N ₆ O ₆
319635	Et	-CH2-	C ₂₀ H ₁₈ N ₄ O ₅
319636	CH2NHAc	-CH2-	C ₂₁ H ₁₉ N ₅ O ₆
319637	CH2NHCOEt	-CH2-	C ₂₂ H ₂₁ N ₅ O ₆
319638	CH2NHCOPr	-CH2-	C ₂₃ H ₂₃ N ₅ O ₆
319639	CH2NHCOBu	-CH2-	C ₂₄ H ₂₅ N ₅ O ₆
319640	cyclobutyl-CONHCH2	-CH2-	C ₂₄ H ₂₃ N ₅ O ₆
319641	Br	-CH2-	C ₁₈ H ₁₃ BrN ₄ O ₅
319642	1-pyrazolyl-CH2	-CH2-	C ₂₂ H ₁₈ N ₆ O ₅

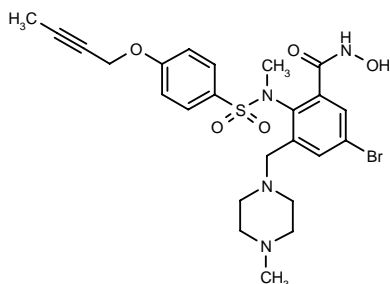
SOURCE – Pfizer.

REFERENCES

1. Bronk, B.S. et al. (Pfizer Products Inc.) *Spiro-pyrimidine-2,4,6-trione metalloproteinase inhibitors*. WO 0234753.

319871

5-Bromo-2-[N-[4-(2-butynyloxy)phenylsulfonyl]-N-methyl-amino]-3-(4-methylpiperazin-1-ylmethyl)benzohydroxamic acid



C24 H29 Br N4 O5 S; Mol wt: 565.4861

ACTION – TNF- α -converting enzyme (TACE) inhibitor (IC_{50} = 25 μ M) with high selectivity relative to MMP-1 (interstitial collagenase; IC_{50} = 1658 μ M); it was able to inhibit TNF- α production in a cellular assay (IC_{50} = 94 μ M) and in murine model, where complete and long-lasting (6 h) inhibition of lipopolysaccharide-stimulated TNF- α production was achieved at the dose of 50 mg/kg p.o. Potentially useful for the treatment of rheumatoid arthritis.

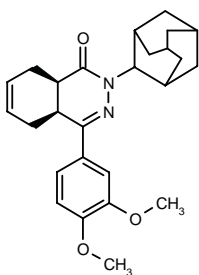
SOURCES – Immunex (Amgen); Wyeth Pharmaceuticals.

REFERENCES

1. Levin, J.I. et al. *Anthranilate sulfonamide hydroxamate TACE inhibitors. Part 2: SAR of the acetylenic P1' group*. Bioorg Med Chem Lett 2002, 12(8): 1199.

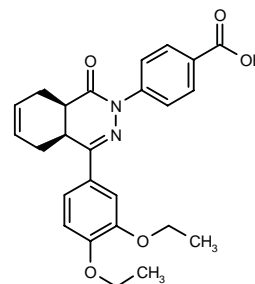
320048^{1,2}

(+)-*cis*-2-(2-Adamantyl)-4-(3,4-dimethoxyphenyl)-1,2,4a,5,8,8a-hexahydrophthalazin-1-one



C26 H32 N2 O3; Mol wt: 420.5498

ACTION – Potent and selective inhibitor of phosphodiesterase type 4 (PDE4; pIC_{50} = 9.3), also proven to inhibit lipopolysaccharide (LPS)-induced TNF- α release in human whole blood (pIC_{30} = 7.05), and to a lesser extent fMLP-induced oxygen radical production in human polymorphonuclear leukocytes (pIC_{35} = 6.82). In mice, a dose of 30 μ mol/kg p.o. reduced acetic acid-induced ear edema by 49%. Potentially useful for the treatment of acute and chronic inflammatory disorders including rheumatoid arthritis and asthma. Another related compound is:



320050²: C25 H26 N2 O5

SOURCE – Byk Gulden (Altana Pharma).

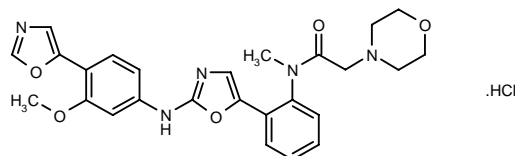
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1. Van der Mey, M. et al. *Novel selective PDE4 inhibitors. 3. In vivo antiinflammatory activity of a new series of N-substituted cis-tetra- and cis-hexahydrophthalazinones*. J Med Chem 2002, 45(12): 2520.

2. Van der Mey, M. et al. *Novel selective phosphodiesterase (PDE4) inhibitors. 4. Resolution, absolute configuration, and PDE4 inhibitory activity of cis-tetra- and cis-hexahydrophthalazinones*. J Med Chem 2002, 45(12): 2526.

BMS-337197**319843**

N-[2-[2-[3-Methoxy-4-(5-oxazolyl)phenylamino]oxazol-5-yl]phenyl]-*N*-methyl-2-(4-morpholinyl)acetamide hydrochloride



C26 H27 N5 O5 . HCl; Mol wt: 525.9902

ACTION – Potent inhibitor of IMP dehydrogenase (inosine monophosphate dehydrogenase, IMPDH) with high selectivity for IMPDH II (IC_{50} = 16 nM, K_i = 3.2 nM) over IMPDH I (IC_{50} = 120 nM). Compound inhibited the proliferation of T-cells (IC_{50} = 0.52 μ M) and normal human peripheral blood mononuclear cells stimulated with anti-CD3 MAb and anti-CD28 MAb (IC_{50} = 130 nM). Preliminary pharmacokinetic studies in rats demonstrated an oral bioavailability of 25%. In a model of antibody production in mice immunized with KLH (keyhole limpet hemocyanin), compound at doses of 50 or 100 mg/kg b.i.d. p.o. was equieffective to once-daily mycophenolate mofetil (CellCept®) in suppressing the humoral immune response. A dose of 100 mg/kg/day almost completely suppressed the development of adjuvant-induced arthritis in rats, without toxicity. Potentially useful as an immunosuppressant for the treatment of rheumatoid arthritis.

SOURCE – Bristol-Myers Squibb.

REFERENCES

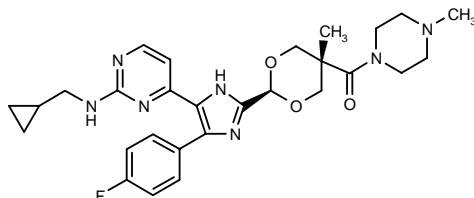
1. Liu, C. et al. (Bristol-Myers Squibb Co.) *Cpds. derived from an amine nucleus that are inhibitors of IMPDH enzyme*. EP 1126843, US 6399773, WO 0025780.

2. Dhar, T.G.M. et al. *Discovery of N-[2-[2-[3-methoxy-4-(5-oxazolyl)phenyl]-amino]-5-oxazolyl]phenyl]-N-methyl-4-morpholineacetamide as a novel and potent inhibitor of inosine monophosphate dehydrogenase with excellent in vivo activity*. J Med Chem 2002, 45(11): 2127.

RPR-238677

319719

trans-*N*-(Cyclopropylmethyl)-4-[4-(4-fluorophenyl)-2-[5-methyl-5-(4-methylpiperazin-1-ylcarbonyl)-1,3-dioxan-2-yl]-1*H*-imidazol-5-yl]pyrimidin-2-amine



C28 H34 F N7 O3; Mol wt: 535.6206

ACTION – Potent, orally available p38 MAP kinase inhibitor (IC_{50} = 4 nM) able to inhibit TNF- α release induced by lipopolysaccharide both *in vitro* and *in vivo*, giving an IC_{50} value of 2 nM in human monocytic cells and an ED_{50} value of 10 mg/kg p.o. in mice. In a streptococcal cell wall-induced arthritis model in rats, compound suppressed paw swelling with an ED_{50} of 10-30 mg/kg p.o., and it also reduced the erosion area and preserved bone anatomy. Potentially useful for the treatment of arthritis.

SOURCE – Aventis Pharma.

REFERENCES

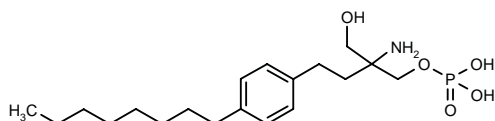
1. Bamborough, P.L. et al. (Rhône-Poulenc Rorer Ltd.) *Imidazolyl-cyclic acetals*. EP 0988301, WO 9856788.

2. McKenna, J.M. et al. *An algorithm-directed two-component library synthesized via solid-phase methodology yielding potent and orally bioavailable p38 MAP kinase inhibitors*. J Med Chem 2002, 45(11): 2173.

IMMUNOMODULATING AGENTS

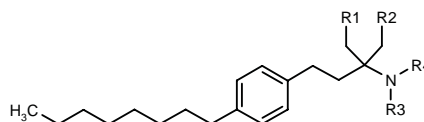
318484

Phosphoric acid 2-amino-2-(hydroxymethyl)-4-(4-octylphenyl)butyl monoester



C19 H34 N O5 P; Mol wt: 387.4536

ACTION – Immunosuppressant, potentially useful for the treatment of autoimmune and inflammatory disorders such as bone marrow and transplant rejection. Other applications include systemic lupus erythematosus, chronic rheumatoid arthritis, diabetes, inflammatory bowel disease, biliary cirrhosis, uveitis, multiple sclerosis, Crohn's disease, ulcerative colitis, bullous pemphigoid, sarcoidosis, psoriasis, autoimmune myositis, Wegener's granulomatosis, ichthyosis, Graves' ophthalmopathy and asthma. Other exemplified phosphate compounds are:



Compound	R1	R2	R3	R4	Formula
318485	OH	CH2CH2PO3H2	H	H	C ₂₁ H ₃₈ NO ₄ P
318486	OH	CH2PO3H2	H	Me	C ₂₁ H ₃₈ NO ₄ P
318487	OH	OPO3H2	Me	Me	C ₂₁ H ₃₈ NO ₅ P
318488	OH	CH2CH2PO3H2	Me	Me	C ₂₃ H ₄₂ NO ₄ P
318489	H	CH2PO3H2	H	H	C ₂₀ H ₃₆ NO ₃ P
318490	H	OPO3H2	H	Me	C ₂₀ H ₃₆ NO ₄ P
318491	H	CH2CH2PO3H2	H	Me	C ₂₂ H ₄₀ NO ₃ P
318492	H	CH2PO3H2	Me	Me	C ₂₂ H ₄₀ NO ₃ P

SOURCE – Merck & Co.

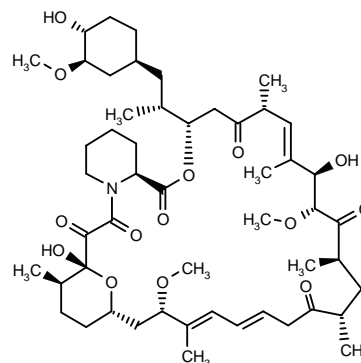
REFERENCES

1. Mandala, S. et al. (Merck & Co., Inc.) *Phosphate derivs. as immunoregulatory agents*. WO 0218395.

318558

(3*S*,6*R*,9*R*,10*R*,12*R*,14*S*,21*S*,23*S*,26*R*,27*R*,34*aS*)-9,27-Dihydroxy-3-[2-[(1*S*,3*R*,4*R*)-4-hydroxy-3-methoxycyclohexyl]-1(*R*)-methylethyl]-10,21-dimethoxy-6,8,12,14,20,26-hexamethyl-3,4,5,6,9,10,11,12,13,14,15,16,21,22,23,24,25,26,27,28,29,31,32,33,34,34*a*-hexacosahydro-1*H*-23,27-epoxypyrido[2,1-*c*][1,4]oxazacyclohentriacontine-1,5,11,15,28,29-hexaone

1-Oxorapamycin



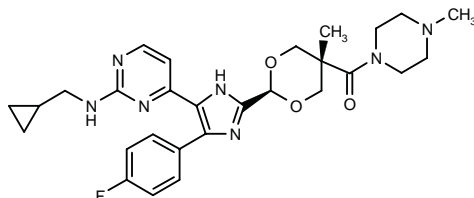
C51 H79 N O14; Mol wt: 930.1781

ACTION – Agent with immunomodulating and neurotrophic activity. *In vitro*, compound demonstrated antifungal and antineoplastic activity, and it was also shown to potentiate nerve growth factor (NGF)-induced outgrowth of neurites in SH-SY5Y cells. Potentially useful for the treatment of transplant rejection, solid tumors, fungal infections, rheumatoid arthritis, multiple sclerosis, restenosis and pulmonary inflammation. By virtue of its neurotrophic activity, its use for stimulating neuronal growth and regeneration, as well as in the treatment of dementia, Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis, spinal cord trauma and sciatic or facial nerve injury, is also described. Other exemplified 1-oxorapamycin derivatives are:

RPR-238677

319719

trans-*N*-(Cyclopropylmethyl)-4-[4-(4-fluorophenyl)-2-[5-methyl-5-(4-methylpiperazin-1-ylcarbonyl)-1,3-dioxan-2-yl]-1*H*-imidazol-5-yl]pyrimidin-2-amine



C28 H34 F N7 O3; Mol wt: 535.6206

ACTION – Potent, orally available p38 MAP kinase inhibitor (IC_{50} = 4 nM) able to inhibit TNF- α release induced by lipopolysaccharide both *in vitro* and *in vivo*, giving an IC_{50} value of 2 nM in human monocytic cells and an ED_{50} value of 10 mg/kg p.o. in mice. In a streptococcal cell wall-induced arthritis model in rats, compound suppressed paw swelling with an ED_{50} of 10-30 mg/kg p.o., and it also reduced the erosion area and preserved bone anatomy. Potentially useful for the treatment of arthritis.

SOURCE – Aventis Pharma.

REFERENCES

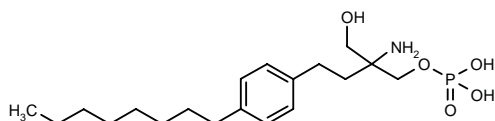
1. Bamborough, P.L. et al. (Rhône-Poulenc Rorer Ltd.) *Imidazolyl-cyclic acetals*. EP 0988301, WO 9856788.

2. McKenna, J.M. et al. *An algorithm-directed two-component library synthesized via solid-phase methodology yielding potent and orally bioavailable p38 MAP kinase inhibitors*. J Med Chem 2002, 45(11): 2173.

IMMUNOMODULATING AGENTS

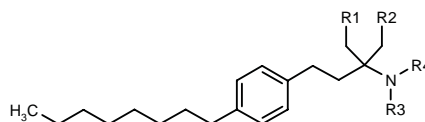
318484

Phosphoric acid 2-amino-2-(hydroxymethyl)-4-(4-octylphenyl)butyl monoester



C19 H34 N O5 P; Mol wt: 387.4536

ACTION – Immunosuppressant, potentially useful for the treatment of autoimmune and inflammatory disorders such as bone marrow and transplant rejection. Other applications include systemic lupus erythematosus, chronic rheumatoid arthritis, diabetes, inflammatory bowel disease, biliary cirrhosis, uveitis, multiple sclerosis, Crohn's disease, ulcerative colitis, bullous pemphigoid, sarcoidosis, psoriasis, autoimmune myositis, Wegener's granulomatosis, ichthyosis, Graves' ophthalmopathy and asthma. Other exemplified phosphate compounds are:



Compound	R1	R2	R3	R4	Formula
318485	OH	CH2CH2PO3H2	H	H	C ₂₁ H ₃₈ NO ₄ P
318486	OH	CH2PO3H2	H	Me	C ₂₁ H ₃₈ NO ₄ P
318487	OH	OPO3H2	Me	Me	C ₂₁ H ₃₈ NO ₅ P
318488	OH	CH2CH2PO3H2	Me	Me	C ₂₃ H ₄₂ NO ₄ P
318489	H	CH2PO3H2	H	H	C ₂₀ H ₃₆ NO ₃ P
318490	H	OPO3H2	H	Me	C ₂₀ H ₃₆ NO ₄ P
318491	H	CH2CH2PO3H2	H	Me	C ₂₂ H ₄₀ NO ₃ P
318492	H	CH2PO3H2	Me	Me	C ₂₂ H ₄₀ NO ₃ P

SOURCE – Merck & Co.

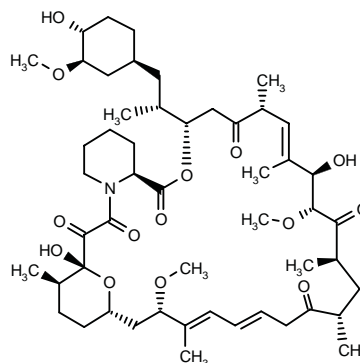
REFERENCES

1. Mandala, S. et al. (Merck & Co., Inc.) *Phosphate derivs. as immunoregulatory agents*. WO 0218395.

318558

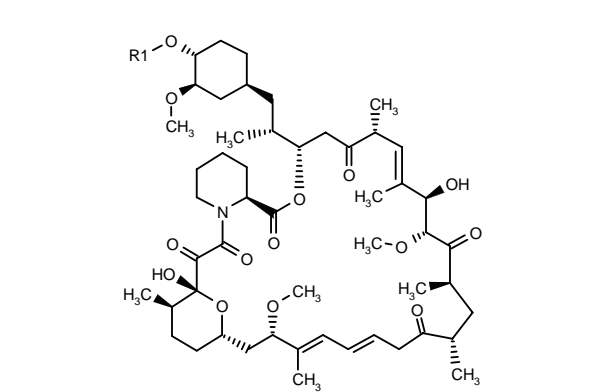
(3*S*,6*R*,9*R*,10*R*,12*R*,14*S*,21*S*,23*S*,26*R*,27*R*,34*aS*)-9,27-Dihydroxy-3-[2-[(1*S*,3*R*,4*R*)-4-hydroxy-3-methoxycyclohexyl]-1(*R*)-methylethyl]-10,21-dimethoxy-6,8,12,14,20,26-hexamethyl-3,4,5,6,9,10,11,12,13,14,15,16,21,22,23,24,25,26,27,28,29,31,32,33,34,34*a*-hexacosahydro-1*H*-23,27-epoxypyrido[2,1-*c*][1,4]oxazacyclohentriacontine-1,5,11,15,28,29-hexaone

1-Oxorapamycin



C51 H79 N O14; Mol wt: 930.1781

ACTION – Agent with immunomodulating and neurotrophic activity. *In vitro*, compound demonstrated antifungal and antineoplastic activity, and it was also shown to potentiate nerve growth factor (NGF)-induced outgrowth of neurites in SH-SY5Y cells. Potentially useful for the treatment of transplant rejection, solid tumors, fungal infections, rheumatoid arthritis, multiple sclerosis, restenosis and pulmonary inflammation. By virtue of its neurotrophic activity, its use for stimulating neuronal growth and regeneration, as well as in the treatment of dementia, Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis, spinal cord trauma and sciatic or facial nerve injury, is also described. Other exemplified 1-oxorapamycin derivatives are:



Compound	R1	Formula
318560	COC(Me)(CH2OH)2	C ₅₆ H ₈₇ NO ₁₇
318562	CH2CH2OH	C ₅₃ H ₈₃ NO ₁₅

SOURCE – Wyeth.

REFERENCES

1. Zhu, T. (American Home Products Corporation) *1-Oxorapamycins*. US 6399625, WO 0226746.

ANTI-C5a MAb

318674

Mouse anti-human C5a monoclonal antibody

ACTION – Anti-C5a monoclonal antibody able to block the C5a-mediated hemolytic response between baboon serum and porcine red blood cells and to significantly prolong xenograft survival in baboons that underwent orthotopic pulmonary xenotransplantation with lungs from CD46 transgenic pigs.

SOURCE – Nextran.

REFERENCES

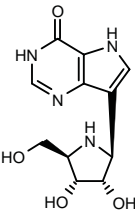
1. Gaca, J.G. et al. *Anti-C5a monoclonal antibody therapy improves pulmonary xenograft survival*. Am J Transplant 2002, 2(Suppl. 3): Abst 167.

BCX-1777

281987

7-[3(S),4(R)-Dihydroxy-5(R)-(hydroxymethyl)pyrrolidin-2(S)-yl]-4,5-dihydro-3H-pyrrolo[3,2-d]pyrimidin-4-one

Immucillin-H



C11 H14 N4 O4; Mol wt: 266.2556

ACTION – T-cell-selective immunosuppressant, a potent and selective inhibitor of purine-nucleoside phosphorylase (IC₅₀ = 1.19 nM against human enzyme) proven to selectively inhibit activated human T-lymphocyte proliferation (IC₅₀ < 0.38 μM) and human T-cell leukemia cell lines (IC₅₀ = 0.4-5 nM). Compound showed an excellent oral bioavailability in mice (63%). In hu-PBL-SCID mice, compound at a dose of 20 mg/kg/day b.i.d. prolonged the life span 2-fold or more compared to vehicle-treated animals. It is undergoing clinical trials for the treatment of T-cell leukemias and lymphomas and may also be useful in other T-cell disorders such as psoriasis.

SOURCES – Albert Einstein College of Medicine, New York, NY (US); BioCryst.

REFERENCES

1. Furneaux, R.H. et al. (Albert Einstein College of Medicine of Yeshiva University; Industrial Research Ltd.) *Inhibitors of nucleoside metabolism*. US 5985848, WO 9919338.

2. Bantia, S. et al. *Purine nucleoside phosphorylase inhibitor BCX-1777 (immucillin-H) - A novel potent and orally active immune suppressive agent*. Int Immunopharmacol 2001, 1(6): 1199.

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4. Evans, G.B. et al. *Synthesis of transition state analogue inhibitors for purine nucleoside phosphorylase and N-riboside hydrolases*. Tetrahedron 2000, 56(19): 3053.

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6. Furneaux, R.H. et al. *Improved syntheses of 3H,5H-pyrrolo[3,2-d]pyrimidines*. J Org Chem 1999, 64(22): 8411.

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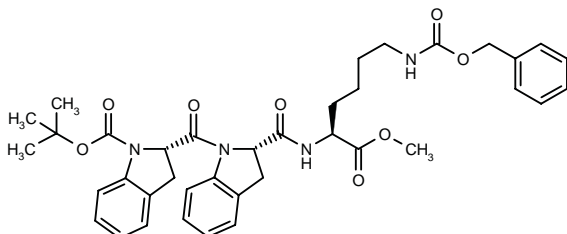
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15. *BioCryst strengthens drug candidate pipeline*. DailyDrugNews.com (Daily Essentials) 2000, Aug 8.

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D-43787***257777**

N^ε-(Benzyloxycarbonyl)-*N*^α-[1-[1-(*tert*-butoxycarbonyl)-indolin-2(*S*)-ylcarbonyl]indolin-2(*S*)-ylcarbonyl]-L-lysine methyl ester



C38 H44 N4 O8; Mol wt: 684.7856

ACTION – Immunosuppressant that binds to the human cyclosporin receptor cyclophilin and inhibits the peptidylprolyl isomerase (PPIase) activity of human cyclophilin ($IC_{50} = 10 \mu M$; IC_{50} cyclosporin = 5 nM), but not the protein phosphatase activity of calcineurin. Compound inhibited T-cell proliferation ($IC_{50} = 0.3 \mu M$) and the production of Th2 cytokines (IL-4, IL-5, IL-13) in T-cells ($IC_{50} = 1.5$ - $1.9 \mu M$ in human peripheral blood mononuclear cells), while being less active against interferon gamma. It also inhibited lipopolysaccharide (LPS)-induced IL-6 and TNF- α production in human monocytes with respective IC_{50} values of 1.2 and 4.7 μM . *In vivo*, compound inhibited late-phase eosinophilia in sensitized guinea pigs (51% inhibition at 10 mg/kg i.p., 66% inhibition at 1 mg/kg by inhalation) and Brown-Norway rats (50% inhibition at 30 mg/kg i.p.). In addition, compound (10-40 mg/kg i.p. b.i.d.) dose-dependently inhibited paw edema in an adjuvant-induced arthritis model in rats with potency comparable to dexamethasone and indomethacin. Potentially useful for the treatment of asthma and arthritis.

SOURCES – Asta Medica; Ivax.

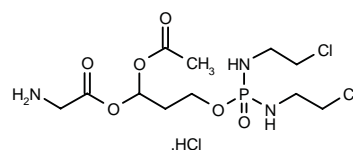
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2. Pahl, A. et al. *Anti-inflammatory effects of a cyclosporine receptor-binding compound, D-43787*. J Pharmacol Exp Ther 2002, 301(2): 738.

*Identified compound **257777** Drug Data Rep 1998, 020(03): 0218.

ONCOLYTIC DRUGS**DNA-DAMAGING DRUGS****320229**

8-Acetoxy-1-chloro-4-(2-chloroethylamino)-10-oxo-5,9-dioxo-3-aza-4-phosphaundecan-11-amine hydrochloride



C11 H22 Cl2 N3 O6 P . HCl; Mol wt: 430.6507

ACTION – Water-soluble prodrug of aldoifosfamide that is transformed to the potent alkylating agent isophosphoramidate mustard in biological systems. Potentially useful for local or regional chemotherapy.

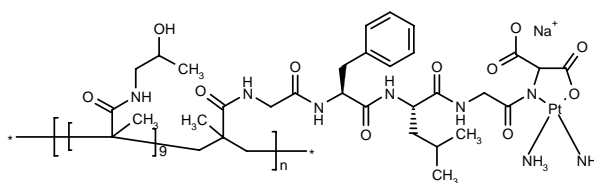
SOURCE – M.D. Anderson Cancer Center, Houston, TX (US).

REFERENCES

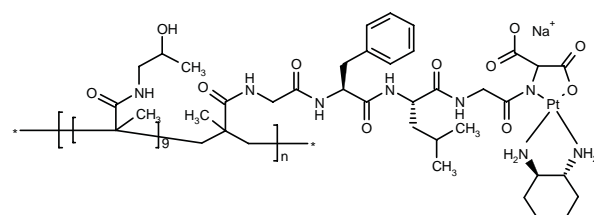
1. Ballatore, C. et al. *Synthesis and biological evaluation of novel mixed acetal prodrugs of aldoifosfamide*. Proc Am Assoc Cancer Res 2002, 43: Abst 286.

AP-5280¹⁻⁹**293448**

cis-Diammine platinum complex polymer composed of an HMPA copolymer bound to an amidomalonate chelator through a Gly-Phe-Leu-Gly linker



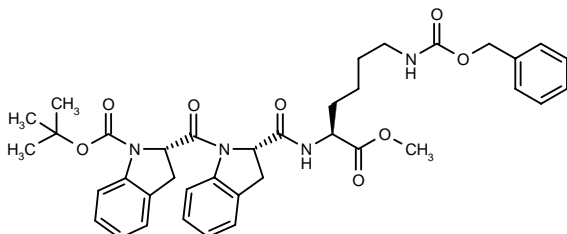
ACTION – Antineoplastic agent, a polymer-linked platinum complex able to inhibit the growth of murine melanoma B16F10 tumors in mice with a therapeutic index 10-fold higher than that of carboplatin. Currently undergoing phase I clinical evaluation. Another related compound is:



AP-5286 [318644]^{4,7}

D-43787***257777**

N^ε-(Benzyloxycarbonyl)-*N*^α-[1-[1-(*tert*-butoxycarbonyl)-indolin-2(*S*)-ylcarbonyl]indolin-2(*S*)-ylcarbonyl]-L-lysine methyl ester



C38 H44 N4 O8; Mol wt: 684.7856

ACTION – Immunosuppressant that binds to the human cyclosporin receptor cyclophilin and inhibits the peptidylprolyl isomerase (PPIase) activity of human cyclophilin ($IC_{50} = 10 \mu M$; IC_{50} cyclosporin = 5 nM), but not the protein phosphatase activity of calcineurin. Compound inhibited T-cell proliferation ($IC_{50} = 0.3 \mu M$) and the production of Th2 cytokines (IL-4, IL-5, IL-13) in T-cells ($IC_{50} = 1.5$ - $1.9 \mu M$ in human peripheral blood mononuclear cells), while being less active against interferon gamma. It also inhibited lipopolysaccharide (LPS)-induced IL-6 and TNF- α production in human monocytes with respective IC_{50} values of 1.2 and $4.7 \mu M$. *In vivo*, compound inhibited late-phase eosinophilia in sensitized guinea pigs (51% inhibition at 10 mg/kg i.p., 66% inhibition at 1 mg/kg by inhalation) and Brown-Norway rats (50% inhibition at 30 mg/kg i.p.). In addition, compound (10-40 mg/kg i.p. b.i.d.) dose-dependently inhibited paw edema in an adjuvant-induced arthritis model in rats with potency comparable to dexamethasone and indomethacin. Potentially useful for the treatment of asthma and arthritis.

SOURCES – Asta Medica; Ivax.

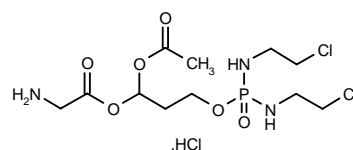
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ONCOLYTIC DRUGS**DNA-DAMAGING DRUGS****320229**

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ACTION – Water-soluble prodrug of aldoifosfamide that is transformed to the potent alkylating agent isophosphoramidate mustard in biological systems. Potentially useful for local or regional chemotherapy.

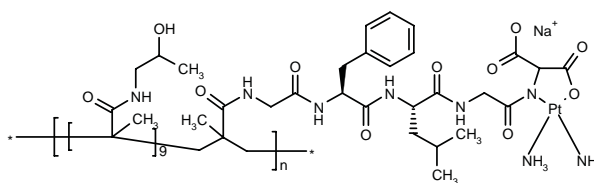
SOURCE – M.D. Anderson Cancer Center, Houston, TX (US).

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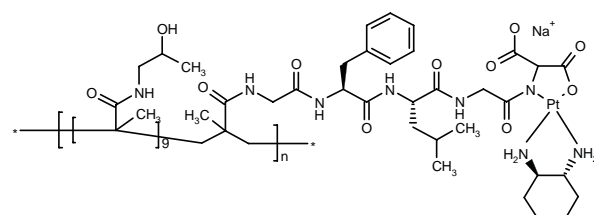
1. Ballatore, C. et al. *Synthesis and biological evaluation of novel mixed acetal prodrugs of aldoifosfamide*. Proc Am Assoc Cancer Res 2002, 43: Abst 286.

AP-5280¹⁻⁹**293448**

cis-Diammine platinum complex polymer composed of an HMPA copolymer bound to an amidomalonate chelator through a Gly-Phe-Leu-Gly linker



ACTION – Antineoplastic agent, a polymer-linked platinum complex able to inhibit the growth of murine melanoma B16F10 tumors in mice with a therapeutic index 10-fold higher than that of carboplatin. Currently undergoing phase I clinical evaluation. Another related compound is:

**AP-5286 [318644]^{4,7}**

SOURCE – Access Pharmaceuticals.

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2. Lin, X. et al. *Effect of treatment schedule on antitumor activity of AP5280, a new platinum polymer.* Proc Am Assoc Cancer Res 2001, 42: Abst 2289.

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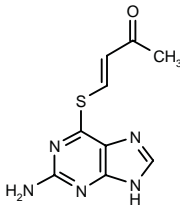
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ANTIMETABOLITES

AVTG

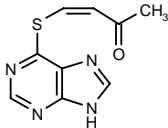
318833

4-(2-Amino-9H-purin-6-ylsulfany)-3(E)-buten-2-one



C9 H9 N5 O S; Mol wt: 235.2701

ACTION – Glutathione-activated 6-thioguanine prodrug with reduced bone marrow toxicity in mice but comparable cytotoxic activity to the parent compound *in vitro* against renal carcinoma ACHN and A-498 cells. Potentially useful for the treatment of tumors with upregulated levels of glutathione. Another related compound is:



AVTP [318835]: C9 H8 N4 O S

SOURCE – University of Wisconsin-Madison, Madison, WI (US).

REFERENCES

1. Gunnarsdottir, S. et al. *Novel glutathione-dependent thiopurine prodrugs: Evidence for enhanced cytotoxicity in tumor cells and for decreased bone marrow toxicity in mice.* J Pharmacol Exp Ther 2002, 301(1): 77.

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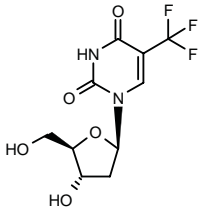
TAS-102

259665

Combination of trifluridine and the reversible inhibitor of thymidine phosphorylase 5-chloro-6-(2-imino-pyrrolidin-1-ylmethyl)uracil hydrochloride in a molar ratio of 1:0.5

TRIFLURIDINE
195553

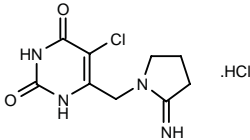
2'-Deoxy-5-(trifluoromethyl)uridine



C10 H11 F3 N2 O5 ; Mol wt: 296.1999

268483+

5-Chloro-6-(2-iminopyrrolidin-1-ylmethyl)uracil hydrochloride



C9 H11 Cl N4 O2 . HCl ; Mol wt: 279.1258

ACTION – Oral combination of trifluridine, an antimetabolite that inhibits thymidylate synthase, and a thymidine phosphorylase inhibitor (TPI) that inhibits the intracellular degradation of trifluridine and prevents the biological functions of TP such as angiogenesis and metastasis. The combination produced an increase in trifluridine levels, thereby increasing cytotoxicity, and was also seen to completely inhibit angiogenesis induced by TP and platelet-derived endothelial cell growth factor (PDGF) in an *in vitro* system. Results of phase I trials in patients with solid tumors indicated that the dose-limiting toxicity was granulocytopenia; preliminary results of an ongoing phase I study in which patients received 100-140 mg/m²/day for 5 days every 21 days showed some cases of disease stabilization for 4-5 months.

SOURCE – Taiho.

REFERENCES

1. Fukushima, M. et al. (Taiho Pharmaceutical Co., Ltd.) *Agents for relieving side effects.* JP 2000273044, WO 0056337.

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3. Hoshino, H. et al. (Taiho Pharmaceutical Co., Ltd.) *Anti-HIV compsns.* JP 2001131075, WO 0134162.

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5. Ryan, K.J. et al. (Department of Health, Education and Welfare) *Alternative synthesis of 2'-deoxy-5-(trifluoromethyl)-uridine and the α-anomer thereof.* US 3531464.

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7. Dwivedy, S. et al. *Safety and pharmacokinetics (PK) of an antitumor/antiangiogenic agent, TAS-102: A phase I study for patients (pts) with solid tumors.* Proc Am Soc Clin Oncol 2001, 20(Part 1): Abst 386.

8. Emura, T. et al. *Invention of a novel antitumor agent, TAS-102 (1): Effect of 5-trifluorothymidine on 5-FU and FdUrd-resistant tumor cells.* Proc Am Assoc Cancer Res 1997, 38: Abst 3175.

9. Hoff, P.M. et al. *Phase I safety and pharmacokinetic study of oral TAS-102 once daily for fourteen days in patients with solid tumors.* Clin Cancer Res 2000, 6(Suppl.): Abst 433.

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11. Miyadera, K. et al. *Newly synthesized thymidine phosphorylase inhibitors inhibit angiogenesis induced by thymidine phosphorylase/PD-ECGF.* Proc Am Assoc Cancer Res 1996, 37: Abst 402.

12. Miyadera, K. et al. *Novel functional antitumor nucleoside TAS-102, combined form of F3dThd and its modulator (2): Inhibitory effect of TPI on tumor-derived angiogenesis and metastasis.* Proc Am Assoc Cancer Res 1998, 39: Abst 4144.

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16. Suzuki, N. et al. *Invention of a novel antitumor agent, TAS-102: (2) Antitumor activities of 5-trifluorothymidine combined with a new inhibitor of thymidine phosphorylase.* Proc Am Assoc Cancer Res 1997, 38: Abst 675.

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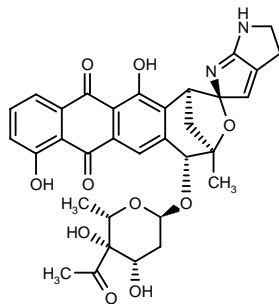
*Drug Data Rep 1999, 021(05): 0459.

ANTIBIOTICS AND ALKALOIDS

KOSINOSTATIN

317146

(1*S*,2*S*,4*R*,5*R*)-8,13-Dihydroxy-4-methyl-7,12-dioxo-1,2,2',4,4',5,5',6',7,12-decahydrospiro[1,4-methano-anthra[2,3-*d*]oxepin-2,2'-pyrrolo[2,3-*b*]pyrrol]-5-yl 4-*C*-acetyl-2,6-dideoxy- α -L-lyxo-hexopyranoside



C33 H32 N2 O10; Mol wt: 616.6198

ACTION – Antineoplastic antibiotic isolated from the actinomycete *Micromonospora* sp. TP-A0468, with strong activity against Gram-positive bacteria (MIC = 0.039 μ g/ml) and moderate activity against Gram-negative bacteria (MIC = 1.56-12.5 μ g/ml). Compound exhibited cytotoxic activity against a panel of human cancer cell lines (IC₅₀ = 0.02-0.55 μ M) and it also inhibited human DNA topoisomerase I and II- α (IC₅₀ = 3-30 μ M).

SOURCES – National Institute Infectious Diseases, Tokyo (JP); Tamagawa University, Tokyo (JP); Toyama Prefectural University, Toyama (JP).

REFERENCES

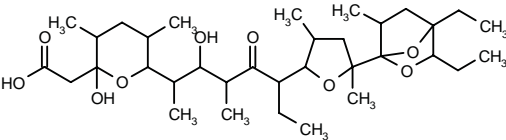
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2. Igarashi, Y. et al. *NMR analysis of quinocycline antibiotics: Structure determination of kosinostatin, an antitumor substance from Micromonospora sp. TP-A0468.* J Antibiot 2002, 55(2): 134.

NK-34896B

318837

2-[6-[5-[5-(3,4-Diethyl-6-methyl-2,7-dioxabicyclo[2.2.1]-hept-1-yl)-3,5-dimethyltetrahydrofuran-2-yl]-2-hydroxy-1,3-dimethyl-4-oxoheptyl]-2-hydroxy-3,5-dimethyl-tetrahydropyran-2-yl]acetic acid



C34 H58 O9; Mol wt: 610.8232

ACTION – Antitumor compound isolated from cultures of *Streptomyces* sp. NA34896 (FERM P-17984) and shown to arrest the cell cycle in the G₁ phase following treatment of human osteosarcoma MG-63 cells.

SOURCE – Nippon Kayaku.

REFERENCES

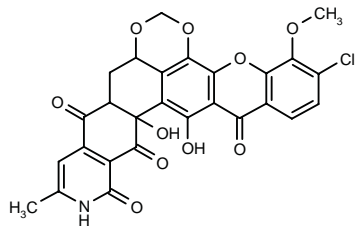
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WSS-2138

320237

3-Chloro-15a,16-dihydroxy-4-methoxy-12-methyl-9,9a,10,13,14,15,15a,17-octahydro-7*H*-xantheno[4',3':2':4,5][1,3]-benzodioxino[7,6-*g*]isoquinoline-10,14,15,17-tetraone



C27 H18 Cl N O10; Mol wt: 551.8892

ACTION – Antitumor compound isolated from cultures of *Streptomyces* sp. TA-0410 (FERM P-17999). WSS-2138 displayed an IC₅₀ < 0.0018 μM against human nasopharyngeal cancer KB cells, and concentration-dependently inhibited the proliferation of HL-60 cells at concentrations below 1 μM.

SOURCES – Sichuan Industrial Institute of Antibiotics, Chengdu (CN); Taisho.

REFERENCES

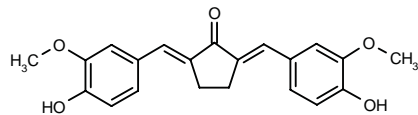
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DNA-INTERCALATING DRUGS

BPR-0Y-007

319809

2,5-Bis(4-hydroxy-3-methoxybenzylidene)cyclopentanone



C21 H20 O5; Mol wt: 352.3840

ACTION – Antineoplastic agent, a potent and selective topoisomerase I inhibitor that also inhibits tubulin polymerization and induces apoptosis in a concentration-dependent manner. Compound showed cytotoxic activity in various human cancer cells, with IC₅₀ values of 1-8 μM; no crossresistance was seen in etoposide-, paclitaxel-, vincristine- and cisplatin-resistant cells.

SOURCE – National Health Research Institutes, Taipei (TW).

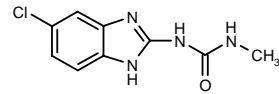
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ANTIMITOTIC DRUGS

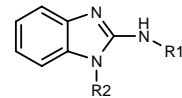
319106

N-(5-Chloro-1*H*-benzimidazol-2-yl)-*N*'-methylurea



C9 H9 Cl N4 O; Mol wt: 224.6501

ACTION – Agent for the treatment of cancer and viral infections that displayed IC₅₀ values of 0.63 and 0.29 μM, respectively, against murine melanoma B16 cells and human colon carcinoma HT-29 cells. This compound was shown to inhibit microtubule formation *in vitro* by 50% at a concentration of 2 μM. Other exemplified compounds are:



Compound	R1	R2	Formula
319107	H	CONHCH2Ph	C ₁₅ H ₁₄ N ₄ O
319108	H	CO2CH2Ph	C ₁₅ H ₁₃ N ₃ O ₂
319109	CONHCH2Ph	H	C ₁₅ H ₁₄ N ₄ O

SOURCE – Procter & Gamble.

REFERENCES

1. Quada, J.C. Jr. et al. (The Procter & Gamble Co.) *Cpds. and methods for use thereof in the treatment of cancer or viral infections.* US 6380232, WO 0226716.

CANCER IMMUNOTHERAPY

HEPTAVALENT KLH CONJUGATE VACCINE

320454

Vaccine consisting of 7 antigens (glycosylated MUC1, globo H, Lewis Y, GM2, Tn[c], sTn[c] and TF[c]) coupled to the carrier protein keyhole limpet hemocyanin (KLH) and formulated with QS-21 or GPI-0100 saponin adjuvants

ACTION – Vaccine for epithelial cancers consisting of 7 antigens coupled to the carrier protein keyhole limpet hemocyanin (KLH) and formulated with adjuvants. The vaccine was well tolerated in mice and induced a strong antibody response against most of the components.

SOURCE – Memorial Sloan-Kettering Cancer Center, New York, NY (US).

REFERENCES

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IGN-101¹⁻⁶

320230

Vaccine based on an alum-adsorbed murine monoclonal antibody as vaccine antigen containing structural epitopes of the carcinoma-associated antigen EpCAM

ACTION – Cancer vaccine that uses an alum-adsorbed murine monoclonal antibody as antigen and contains structural epitopes of the carcinoma-associated antigen epithelial cell adhesion molecule (EpCAM), designed to attack disseminated tumor cells causing disease spread. In rhesus monkeys, the vaccine induced an immune response against EpCAM without side effects. Results from a phase I trial in patients with epithelial cancers likely to express EpCAM showed that the vaccine (500 µg on days 1, 15, 29 and 57) induced EpCAM-specific IgG in 10 of 19 patients and decreased the number of circulating EpCAM+ cells. No objective tumor responses were obtained, but 15 patients had stable disease for at least 2 months. Side effects consisted of mild and transient reactions at the injection site. The vaccine was advanced to a phase II/III trial for non-small cell lung cancer. Another related vaccine is:

Vaccine formulation based on an antiidiotypic murine monoclonal antibody capable of inducing an anti-Lewis Y immune response

IGN-301 [320236]^{5,6}

SOURCE – Igneon.

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5. Waxenecker, G. et al. *Qualitative and quantitative dissection of the immune response to the cancer vaccine candidates IGN101 and IGN301*. Proc Am Assoc Cancer Res 2002, 43: Abst 2779.

6. *Product Pipeline*. Igneon Web Site 2002, May 30.

TF(c)–KLH CONJUGATE VACCINE

320451

Vaccine based on the Thomsen-Friedenreich (TF[c]) antigen coupled to the carrier protein keyhole limpet hemocyanin (KLH) and formulated with QS-21 adjuvant

ACTION – Prostate cancer vaccine consisting of Thomsen-Friedenreich cluster (TF[c]) antigen covalently linked to KLH (keyhole limpet hemocyanin), and mixed with the immunological adjuvant QS-21. A preliminary clinical trial in patients with prostate cancer who failed primary treatment with radiation or surgery showed that the vaccine was well tolerated, induced high titers of IgM and IgG antibodies and possessed an antitumor effect.

SOURCE – Memorial Sloan-Kettering Cancer Center, New York, NY (US).

REFERENCES

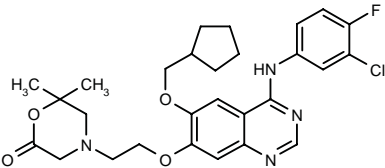
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2. Slovin, S.F. et al. *Thomsen-Friedenreich cluster [TF(c)]-KLH conjugate vaccine plus the immunological adjuvant QS21 in prostate cancer (PC) patients in the minimal disease state*. Proc Am Assoc Cancer Res 2002, 43: Abst 2780.

INHIBITORS OF SIGNAL
TRANSDUCTION PATHWAYS

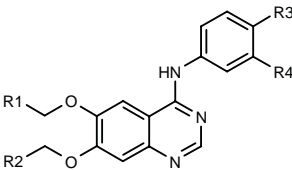
318308

4-[2-[4-(3-Chloro-4-fluorophenylamino)-6-(cyclopentyl-methoxy)quinazolin-7-yloxy]ethyl]-6,6-dimethylmorpholin-2-one



C28 H32 Cl F N4 O4; Mol wt: 543.0358

ACTION – Agent with protein tyrosine kinase-inhibitory activity, expected to be useful for the treatment of cancer, polyps and disorders of the respiratory tract, gastro-intestinal tract, gallbladder, kidney and skin. Other exemplified bicyclic compounds are:



Compound	R1	R2	R3	R4	Formula
318309	cyclopropyl	5-oxo-3-THF-N(Me)CH2	F	Cl	C ₂₅ H ₂₆ ClFN ₄ O ₄
318310	(S)-6-Me-2-oxo-4-morpholinyl-CH2	H	H	Br	C ₂₂ H ₂₃ BrN ₄ O ₄
318311	(S)-t-BuOCOCH2N-[CH2CH(OH)Me]CH2	H	H	Br	C ₂₆ H ₃₃ BrN ₄ O ₅

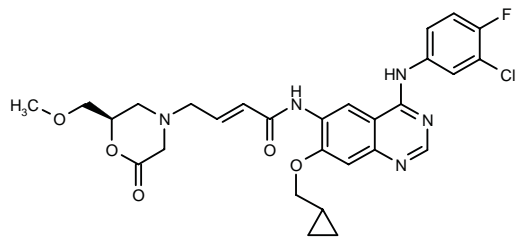
SOURCE – Boehringer Ingelheim.

REFERENCES

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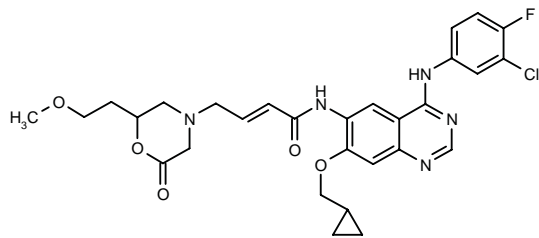
318315

N-[4-(3-Chloro-4-fluorophenylamino)-7-(cyclopropylmethoxy)quinazolin-6-yl]-4-[2(*R*)-(methoxymethyl)-6-oxomorpholin-4-yl]-2-butenamide



C28 H29 Cl F N5 O5; Mol wt: 570.0181

ACTION – Agent with protein tyrosine kinase-inhibitory activity, expected to be useful for the treatment of cancer, polyps and disorders of the respiratory tract, gastro-intestinal tract, gallbladder, kidney and skin. Another exemplified bicyclic compound is:



318317: C29 H31 Cl F N5 O5

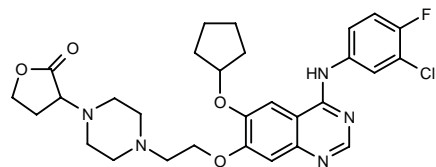
SOURCE – Boehringer Ingelheim.

REFERENCES

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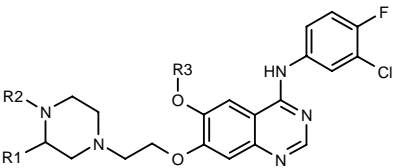
318325

3-[4-[2-[4-(3-Chloro-4-fluorophenylamino)-6-(cyclopentyloxy)quinazolin-7-yloxy]ethyl]piperazin-1-yl]tetrahydrofuran-2-one

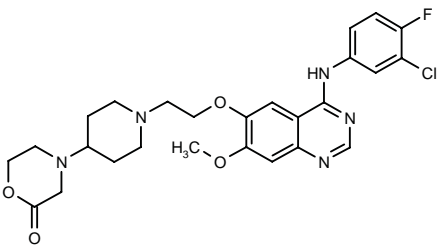


C29 H33 Cl F N5 O4; Mol wt: 570.0617

ACTION – Agent with protein tyrosine kinase-inhibitory activity, expected to be useful for the treatment of cancer, polyps and disorders of the respiratory tract, gastrointestinal tract, gallbladder, kidney and skin. Other exemplified bicyclic compounds are:



Compound	R1	R2	R3	Formula
318326	H	(S)-5-oxo-2-THF-CO	cyclopentyl-CH2	C ₃₁ H ₃₅ ClFN ₅ O ₅
318337	H	5-oxo-3-THF-CO	cyclopentyl-CH2	C ₃₁ H ₃₅ ClFN ₅ O ₅
318338	H	(R)-5-oxo-2-THF-CH2	cyclopentyl	C ₃₀ H ₃₅ ClFN ₅ O ₄
318340		-CH2OCOCH2-	cyclopropyl-CH2	C ₂₇ H ₂₉ ClFN ₅ O ₄



318341: C26 H29 Cl F N5 O4

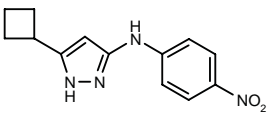
SOURCE – Boehringer Ingelheim.

REFERENCES

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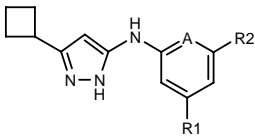
318327

5-Cyclobutyl-N-(4-nitrophenyl)-1*H*-pyrazol-3-amine

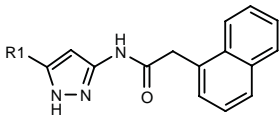


C13 H14 N4 O2; Mol wt: 258.2796

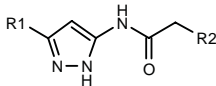
ACTION – Inhibitor of protein kinases, particularly cyclin-dependent kinases CDK2 and CDK5 and glycogen synthase kinase-3 (GSK-3). Potentially useful for the treatment of proliferative and neurodegenerative disorders, as well as male infertility, diabetes, impaired glucose tolerance, syndrome X, polycystic ovary syndrome, obesity, frailty, age-related decline in physical performance, acute sarcopenia, sepsis, hair loss and immuno-deficiency. Other exemplified pyrazole derivatives are:



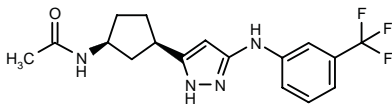
Compound	R1	R2	A	Formula
318328	CF3	CF3	CH	C ₁₅ H ₁₃ F ₈ N ₃
318329	H	Cl	N	C ₁₂ H ₁₃ ClN ₄



Compound	R1	Formula
318332	cis-3-(cyclopropyl-CH2CONH)-cyclobutyl	C ₂₄ H ₂₆ N ₄ O ₂
318334	(S)-2-benzothiazolyl-OCH(Me)	C ₂₄ H ₂₀ N ₄ O ₂ S



Compound	R1	R2	Formula
318331	3-AcNH-cyclopentyl	1-Naph	C ₂₂ H ₂₄ N ₄ O ₂
318335	cis-3-(2-MeO-Ph)-cyclobutyl	6-quinolyl	C ₂₅ H ₂₄ N ₄ O ₂
318336	cis-3-(4-Me-Ph)-cyclobutyl	1-Naph	C ₂₆ H ₂₅ N ₃ O



318330: C17 H19 F3 N4 O

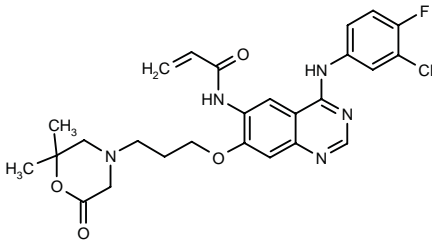
SOURCE – Pfizer.

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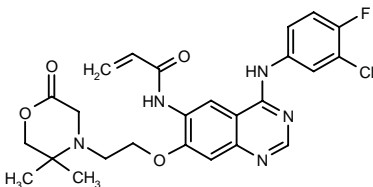
318344

N-[4-(3-Chloro-4-fluorophenylamino)-7-[3-(2,2-dimethyl-6-oxomorpholin-4-yl)propoxy]quinazolin-6-yl]acrylamide



C26 H27 Cl F N5 O4; Mol wt: 527.9813

ACTION – Agent with protein tyrosine kinase-inhibitory activity, expected to be useful for the treatment of cancer, polyps and disorders of the respiratory tract, gastro-intestinal tract, gallbladder, kidney and skin. Another exemplified quinazoline is:



318346: C25 H25 Cl F N5 O4

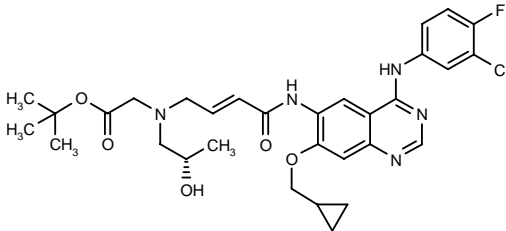
SOURCE – Boehringer Ingelheim.

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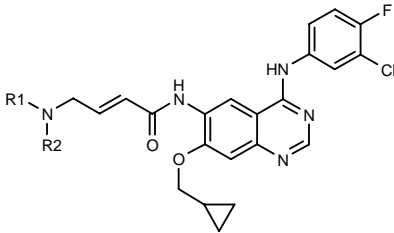
318352

2-[N-[4-[4-(3-Chloro-4-fluorophenylamino)-7-(cyclopropylmethoxy)quinazolin-6-ylamino]-4-oxo-2-butenyl]-N-[2(S)-hydroxypropyl]amino]acetic acid *tert*-butyl ester



C31 H37 Cl F N5 O5; Mol wt: 614.1143

ACTION – Agent with protein tyrosine kinase-inhibitory activity, expected to be useful for the treatment of cancer, polyps and disorders of the respiratory tract, gastro-intestinal tract, gallbladder, kidney and skin. Other exemplified quinazoline derivatives are:



Compound	R1	R2	Formula
318354	-(S)CH2CH(Me)OCOCH2-		C ₂₇ H ₂₇ ClFN ₅ O ₄
318355	CH2CO2H	(R)-CH2CH(OH)Me	C ₂₇ H ₂₉ ClFN ₅ O ₅
318357	CH2CO2Me	(R)-CH2CH(OH)Me	C ₂₈ H ₃₁ ClFN ₅ O ₅

SOURCE – Boehringer Ingelheim.

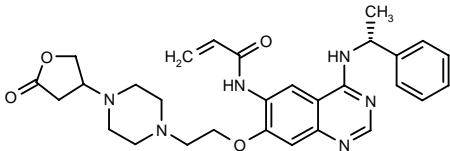
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318442

N-[7-[2-[4-(5-Oxotetrahydrofuran-3-yl)piperazin-1-yl]ethoxy]-4-[1 (*R*)-phenylethylamino]quinazolin-6-yl]acrylamide

N-[7-[2-[4-(5-Oxotetrahydrofuran-3-yl)piperazin-1-yl]ethoxy]-4-[1 (*R*)-phenylethylamino]quinazolin-6-yl]-2-propenamide



C29 H34 N6 O4; Mol wt: 530.6256

ACTION – An inhibitor of tyrosine kinases, particularly epidermal growth factor receptor (EGFR) tyrosine kinase, which was shown to inhibit the proliferation of F/L-HERc cells with an IC₅₀ of 12 nM. Potentially useful for the treatment of cancer and polyps, as well as disorders of the respiratory tract, gastrointestinal tract, gallbladder, kidney and skin.

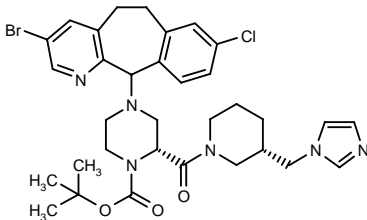
SOURCE – Boehringer Ingelheim.

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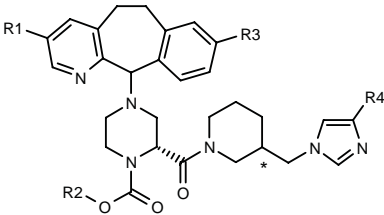
318804

4-(3-Bromo-8-chloro-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-yl)-2(*R*)-[3(*R*)-(1*H*-imidazol-1-ylmethyl)piperidin-1-ylcarbonyl]piperazine-1-carboxylic acid *tert*-butyl ester

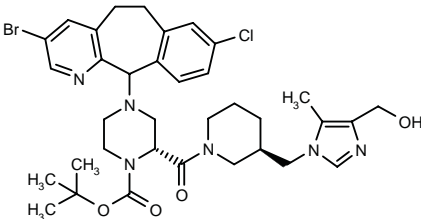


C33 H40 Br Cl N6 O3; Mol wt: 684.0750

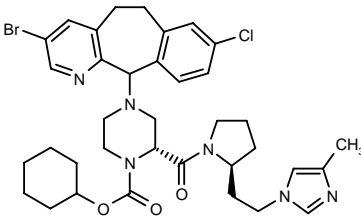
ACTION – Protein farnesyltransferase inhibitor (IC₅₀ < 0.04-2.7 nM). Potentially useful as an antiproliferative agent in the treatment of pancreatic cancer, lung cancer, myeloid leukemia, thyroid cancer, myelodysplastic tumor, epidermal carcinoma, colon cancer, melanoma, breast cancer and prostate cancer. Other exemplified piperazinyl-substituted tricyclic compounds include the following:



Compound	R1	R2	R3	R4	*Isomer	Formula
318805	H	t-Bu	Cl	H	R	C ₃₃ H ₄₁ ClN ₆ O ₃
318806	H	i-Pr	Cl	Me	S	C ₃₃ H ₄₁ ClN ₆ O ₃
318807	Br	t-Bu	Cl	Me	S	C ₃₄ H ₄₂ BrClN ₆ O ₃
318810	Cl	t-Bu	H	Me	R	C ₃₄ H ₄₃ ClN ₆ O ₃
318812	Br	cyclohexyl	H	Me	R	C ₃₆ H ₄₅ BrN ₆ O ₃
318813	H	cyclohexyl	Cl	H		C ₃₆ H ₄₅ ClN ₆ O ₃



318808: C35 H44 Br Cl N6 O4



318809: C36 H44 Br Cl N6 O3

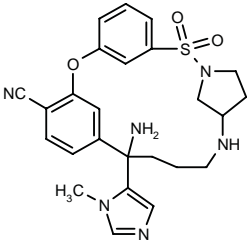
SOURCE – Schering-Plough.

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318967

11-Amino-11-(1-methyl-1*H*-imidazol-5-yl)-2,2-dioxo-17-oxa-2-thia-3,7-diazatetracyclo[16.3.1.1^{3,6}.1^{12,16}]-tetracos-1(22),12(23),13,15,18,20-hexaene-15-carbonitrile

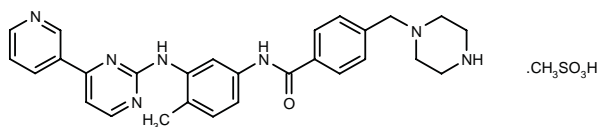


C25 H28 N6 O3 S; Mol wt: 492.6012

ACTION – Macrocyclic compound able to inhibit protein farnesyltransferase and/or protein geranylgeranyl-transferase. Potentially useful for the treatment of cancer, as well as other disorders including blindness related to retinal vascularization, hepatitis delta infections, restenosis and polycystic kidney disease. Other specifically claimed compounds are:

319350

N-[4-Methyl-3-[4-(3-pyridyl)pyrimidin-2-ylamino]phenyl]-4-(piperazin-1-ylmethyl)benzamide methanesulfonate



C₂₈ H₂₉ N₇ O . C H₄ O₃ S; Mol wt: 575.6907

ACTION – A specifically claimed compound from a series of *N*-phenylpyrimidin-2-amine derivatives that inhibit PDGF (platelet-derived growth factor) receptor kinase. Potentially useful for the treatment of cancer, as well as nonmalignant proliferative disorders including atherosclerosis, thrombosis, psoriasis, scleroderma, fibrosis and asthma. The use of this compound for protecting stem cells and for treating the hemotoxic effects of chemotherapeutic agents is also described.

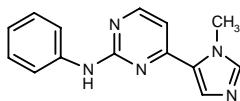
SOURCE – Novartis.

REFERENCES

1. Buerger, H.M. et al. (Novartis AG;Novartis-Erfindungen VmbH) *N*-Phenyl-2-pyrimidine-amine derivs. WO 0222597.

319354

4-(1-Methyl-1*H*-imidazol-5-yl)-*N*-phenylpyrimidin-2-amine



C₁₄ H₁₃ N₅; Mol wt: 251.2917

ACTION – A representative compound from a series of 4-(1*H*-imidazol-5-yl)-2-(phenylamino)pyrimidine derivatives that acts as an inhibitor of cyclin-dependent kinase CDK2 (IC₅₀ = 0.146 μM). Potentially useful for the treatment of proliferative disorders including cancer, psoriasis, rheumatoid arthritis, Kaposi's sarcoma, hemangioma, acute and chronic nephropathies, atherosclerosis, arterial restenosis, autoimmune diseases, acute and chronic inflammation, bone diseases and ocular diseases with retinal vessel proliferation.

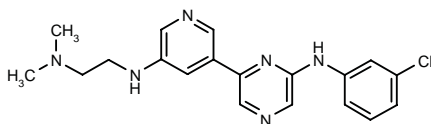
SOURCE – AstraZeneca.

REFERENCES

1. Breault, G.A. et al. (AstraZeneca AB;AstraZeneca plc) *Imidazo-5-yl-2-anilino-pyrimidines as agents for the inhibition of the cell proliferation*. WO 0220512.

319445

*N*¹-[5-[6-(3-Chlorophenylamino)pyrazin-2-yl]pyridin-3-yl]-*N*²,*N*²-dimethylethane-1,2-diamine



C₁₉ H₂₁ Cl N₆; Mol wt: 368.8699

ACTION – A selective inhibitor of VEGF (vascular endothelial growth factor) receptor tyrosine kinase (IC₅₀ = 0.07 μM) with selectivity over cyclin-dependent kinases (CDKs). It demonstrated cytotoxicity *in vitro* against a panel of cancer cell lines, and *in vivo* following i.p. administration to mice bearing human malignant melanoma A-375 xenografts. Potentially useful for the treatment of cancer, diabetic retinopathy, rheumatoid arthritis, endometriosis and psoriasis.

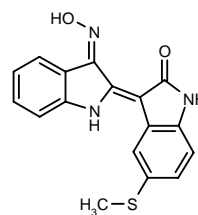
SOURCE – Ortho-McNeil.

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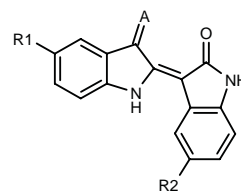
319543

2-[5-(Methylsulfanyl)-2-oxo-2,3-dihydro-1*H*-indol-3-ylidene]-2,3-dihydro-1*H*-indol-3-one oxime



C₁₇ H₁₃ N₃ O₂ S; Mol wt: 323.3747

ACTION – An inhibitor of cyclin-dependent kinases (CDKs) and/or glycogen synthase kinase-3β (GSK-3β), with an IC₅₀ of 0.02 μM against CDK2 and shown to exert antiproliferative activity against human breast cancer MCF7 (IC₅₀ = 0.7 μM), non-small cell lung cancer NCI-H460 (IC₅₀ = 1.0 μM), colon carcinoma HCT 116 (IC₅₀ = 0.6 μM) and prostate carcinoma DU 145 tumor cells (IC₅₀ = 1.0 μM). Potentially useful for the treatment of cancer, autoimmune diseases, chemotherapy-induced mucositis and alopecia, cardiovascular disorders, infections, renal disorders, and chronic and acute neurodegenerative diseases. Other sulfur-containing indirubin derivatives are:



Compound	R1	R2	A	Formula
319544	NHAc	SMe	O	C ₁₉ H ₁₅ N ₃ O ₃ S
319546	H	SOMe	O	C ₁₇ H ₁₂ N ₂ O ₃ S
319547	H	SOMe	N(OH)	C ₁₇ H ₁₃ N ₃ O ₃ S

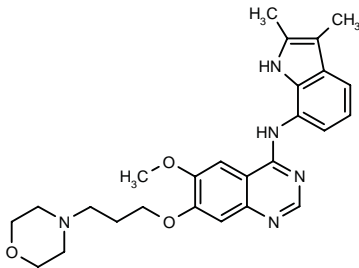
SOURCE – Schering AG.

REFERENCES

1. Prien, O. et al. (Schering AG) *Sulphur-containing indirubin derivs., production and use thereof*. DE 10053474, WO 0234717.

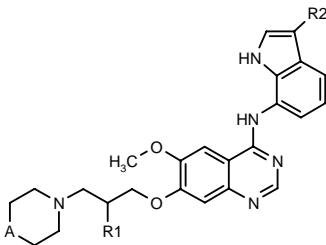
319548

N-(2,3-Dimethyl-1*H*-indol-7-yl)-6-methoxy-7-[3-(4-morpholinyl)propoxy]quinazolin-4-amine



C26 H31 N5 O3; Mol wt: 461.5629

ACTION – An inhibitor of the nonreceptor tyrosine kinases Src and/or c-Yes, with little activity against receptor tyrosine kinases such as VEGF (vascular endothelial growth factor) or EGF (epidermal growth factor) tyrosine kinases. Potentially useful for the treatment of solid tumors. Other exemplified quinazoline derivatives are:



Compound	R1	R2	A	Formula
319549	H	H	O	C ₂₄ H ₂₇ N ₅ O ₃
319550	H	Cl	O	C ₂₄ H ₂₆ ClN ₅ O ₃
319551	OAc	Cl	O	C ₂₆ H ₂₈ ClN ₅ O ₅
319552	OH	Cl	O	C ₂₄ H ₂₆ ClN ₅ O ₄
319553	OH	Cl	CH	C ₂₆ H ₂₈ ClN ₅ O ₃

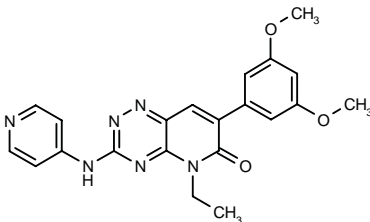
SOURCE – AstraZeneca.

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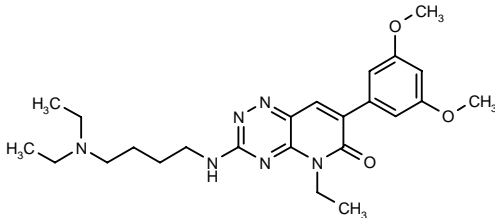
319673

7-(3,5-Dimethoxyphenyl)-5-ethyl-3-(pyridin-4-ylamino)-pyrido[2,3-*e*][1,2,4]triazin-6(5*H*)-one



C21 H20 N6 O3; Mol wt: 404.4280

ACTION – An inhibitor of cyclin-dependent kinases and/or tyrosine kinases shown to be active against fibroblast growth factor receptor (FGFR; IC₅₀ = 1.22 μM) and vascular endothelial growth factor receptor-2 (VEGFR-2; IC₅₀ = 0.35 μM) kinases. Potentially useful for the treatment of cancer, psoriasis, atherosclerosis, diabetic retinopathy, angiogenesis, restenosis, and immune disorders including asthma, rheumatoid arthritis, type 1 diabetes and transplant rejection. Another exemplified compound is:



319674: C24 H34 N6 O3

SOURCE – Pfizer.

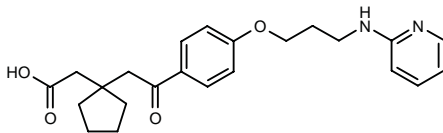
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ANGIOGENESIS INHIBITORS

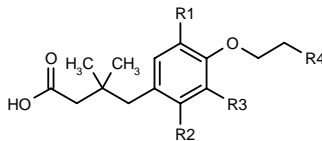
318314

2-[1-[2-Oxo-2-[4-[3-(pyridin-2-ylamino)propoxy]phenyl]-ethyl]cyclopentyl]acetic acid

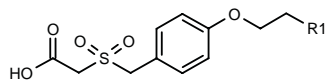


C23 H28 N2 O4; Mol wt: 396.4842

ACTION – Integrin α_vβ₃ and/or α_vβ₅ receptor antagonist, potentially useful for the treatment of cancer, as well as angiogenesis, osteoporosis, humoral hypercalcemia, smooth muscle cell migration, restenosis, atherosclerosis, macular degeneration, retinopathy and arthritis. Other specifically claimed 1,1-disubstituted cycloalkyl compounds include the following:



Compound	R1	R2	R3	R4	Formula
318316	H	H	H	6-NH2-2-Pyr	C ₁₉ H ₂₄ N ₂ O ₃
318320	H	H	Br	2-Pyr-NHCH2	C ₂₀ H ₂₅ BrN ₂ O ₃
318321	H	H	CO2H	2-Pyr-NHCH2	C ₂₁ H ₂₆ N ₂ O ₅
318322	F	H	Br	2-Pyr-NHCH2	C ₂₀ H ₂₄ BrFN ₂ O ₃
318323	H	H	Cl	2-Pyr-NHCH2	C ₂₀ H ₂₅ ClN ₂ O ₃
318324	H	ethynyl	H	2-Pyr-NHCH2	C ₂₂ H ₂₆ N ₂ O ₃



Compound	R1	Formula
318318	2-Pyr-NHCH2	C ₁₇ H ₂₀ N ₂ O ₅ S
318319	6-MeNH-2-Pyr	C ₁₇ H ₂₀ N ₂ O ₅ S

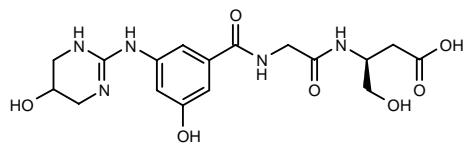
SOURCE – Pharmacia.

REFERENCES

1. Khanna, I.K. et al. (Pharmacia Corp.) *Gem-substd. αvβ3 integrin antagonists*. WO 0218340.

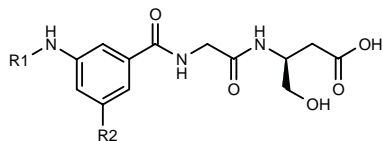
318565

4-Hydroxy-3(S)-[N-[3-hydroxy-5-(5-hydroxy-1,4,5,6-tetrahydropyrimidin-2-ylamino)benzoyl]glycylamino]-butyric acid



C17 H23 N5 O7; Mol wt: 409.3967

ACTION – An inhibitor of α_vβ₃ and/or α_vβ₅ integrin receptors, potentially useful for the treatment of cancer, angiogenesis, osteoporosis, humoral hypercalcemia, smooth muscle cell migration, restenosis, atherosclerosis, macular degeneration, retinopathy and arthritis. Other specifically claimed hydroxy acid compounds are:



Compound	R1	R2	Formula
318566	1,4,5,6-tetrahydro-2-pyrimidinyl	OH	C ₁₇ H ₂₃ N ₅ O ₆
318567	5-OH-1,4,5,6-tetrahydro-2-pyrimidinyl	H	C ₁₇ H ₂₃ N ₅ O ₆
318568	1,4,5,6-tetrahydro-2-pyrimidinyl	H	C ₁₇ H ₂₃ N ₅ O ₅
318570	C(=NH)NH2	CF3	C ₁₅ H ₁₈ F ₃ N ₅ O ₅
318571	5-F-1,4,5,6-tetrahydro-2-pyrimidinyl	OH	C ₁₇ H ₂₂ FN ₅ O ₆
318572	5-F-1,4,5,6-tetrahydro-2-pyrimidinyl	H	C ₁₇ H ₂₂ FN ₅ O ₅

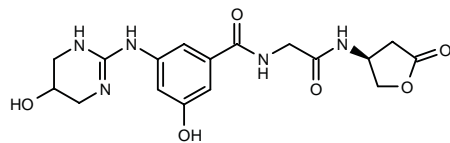
SOURCE – Pharmacia.

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1. Rogers, T. et al. (Pharmacia Corp.) *Hydroxy acid integrin antagonists*. WO 0226717.

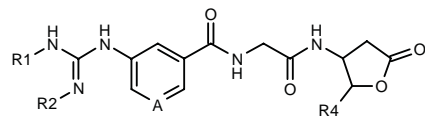
318888

3-Hydroxy-5-(5-hydroxy-1,4,5,6-tetrahydropyrimidin-2-yl-amino)-N-[N-[5-oxotetrahydrofuran-3(S)-yl]carbamoyl-methyl]benzamide



C17 H21 N5 O6; Mol wt: 391.3819

ACTION – Integrin α_vβ₃ and/or α_vβ₅ antagonist considered to have potential in the treatment of cancer, angiogenesis, osteoporosis, humoral hypercalcemia, smooth muscle cell migration, restenosis, atherosclerosis, macular degeneration, retinopathy and arthritis. Other exemplified compounds include the following:



Compound	R1	R2	R4	A	Isomer	Formula
318889	-CH2CH(OH)CH2-		H	CH	S	C ₁₇ H ₂₁ N ₅ O ₅
318890	H	H	H	C(CF3)	S	C ₁₅ H ₁₆ F ₃ N ₅ O ₄
318891	-CH2CHFCH2-		H	CH	S	C ₁₇ H ₂₀ FN ₅ O ₄
318892	-CH2CH(OH)CH2-		H	N	S	C ₁₆ H ₂₀ N ₆ O ₅
318893	-CH2CH(OH)CH2-		allyl	C(OH)		C ₂₀ H ₂₅ N ₅ O ₆
318894	-CH2CH(OH)CH2-		ethynyl	C(OH)		C ₁₉ H ₂₁ N ₅ O ₆
318895	-CH2CH(OH)CH2-		C10H21	C(OH)		C ₂₇ H ₄₁ N ₅ O ₆
318896	-CH2CH(OH)CH2-		4-F-Ph	C(OH)		C ₂₃ H ₂₄ FN ₅ O ₆

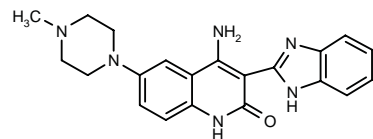
SOURCE – Pharmacia.

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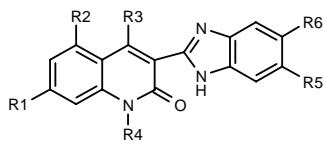
319398

4-Amino-3-(1H-benzimidazol-2-yl)-6-(4-methylpiperazin-1-yl)quinolin-2(1H)-one

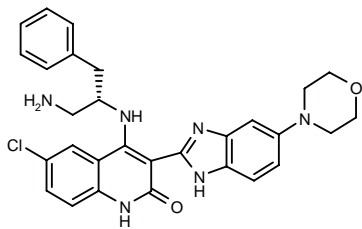


C21 H22 N6 O; Mol wt: 374.4458

ACTION – Inhibitor of receptor tyrosine kinases, particularly bFGF (basic fibroblast growth factor) and VEGF (vascular endothelial growth factor) kinases. By virtue of its antiangiogenic activity, it is considered useful for the treatment of cancer. Other exemplified quinolinone derivatives are:



Compound	R1	R2	R3	R4	R5	R6	Formula
319399	H	H	OH	CH2Ph	H	H	C ₂₃ H ₁₇ N ₃ O ₂
319400	H	H	NH2	H	Me	4-morpholinyl	C ₂₁ H ₂₁ N ₅ O ₂
319402	H	OMe	NH2	H	H	Me	C ₁₈ H ₁₆ N ₄ O ₂
319405	H	H	H	H	H	CON(Me)2	C ₁₉ H ₁₆ N ₄ O ₂
319407	OMe	H	3(S)-quinuclidinyl-NH	H	H	H	C ₂₄ H ₂₆ N ₅ O ₂



319408: C29 H29 Cl N6 O2

SOURCE – Chiron.

REFERENCES

1. Renhowe, P. et al. (Chiron Corp.) *Quinolizone derivs.* WO 0222598.

319585

L-Glutaminyl-L-lysyl-L-arginyl-L-lysyl-L-arginyl-L-lysyl-L-lysyl-L-seryl-L-arginyl-L-tyrosyl-L-lysyl-L-seryl-L-tryptophyl-L-seryl-L-valyl-L-proline

C92 H156 N32 O22; Mol wt: 2062.4460

ACTION – Peptide corresponding to a fragment of the vascular endothelial growth factor (VEGF) sequence, able to antagonize the VEGF receptor and exert antiangiogenic activity. Potentially useful for the treatment of cancer.

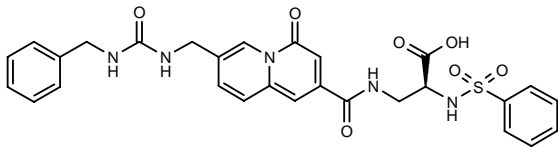
SOURCE – Ark Therapeutics.

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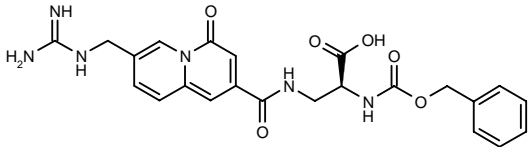
319815

3-[7-(3-Benzylureidomethyl)-4-oxo-4H-quinolizin-2-ylcarboxamido]-2(S)-(phenylsulfonamido)propionic acid



C28 H27 N5 O7 S; Mol wt: 577.6153

ACTION – Integrin $\alpha_v\beta_3$ receptor antagonist (IC_{50} = 6 nM) with > 800-fold selectivity over integrin $\alpha_{IIb}\beta_3$ receptors (IC_{50} = 4850 nM), potentially useful as an angiogenesis inhibitor for the treatment of cancer. Another related compound is:



319814: C23 H24 N6 O6

SOURCE – Shire BioChem.

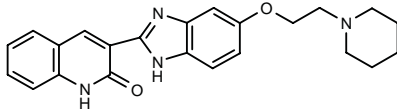
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2. Rej, R. et al. *Synthesis and in vitro potency of quinolizone-based $\alpha_v\beta_3$ receptor antagonists.* Proc Am Assoc Cancer Res 2002, 43: Abst 3669.

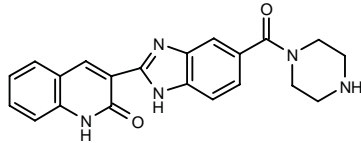
319816

3-[5-[2-(1-Piperidinyl)ethoxy]-1H-benzimidazol-2-yl]-quinolin-2(1H)-one



C23 H24 N4 O2; Mol wt: 388.4686

ACTION – Angiogenesis inhibitor, a potent and selective vascular endothelial growth factor receptor VEGFR-2 (KDR) kinase inhibitor (IC_{50} = 3 nM) with strong activity against VEGF-stimulated human umbilical vein endothelial cell mitogenesis (IC_{50} = 18 nM). It inhibited KDR phosphorylation in mouse lung (IC_{50} = 130 nM) and was active in a Matrigel angiogenesis model and against human fibrosarcoma HT-1080 xenografts in mice. Another related compound is:



319817: C21 H19 N5 O2

SOURCE – Merck & Co.

REFERENCES

1. Fraley, M.E. et al. (Merck & Co., Inc.) *Tyrosine kinase inhibitors.* WO 0128993.

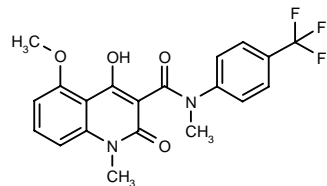
2. Fraley, M.E. et al. *Design, synthesis, and in vitro/in vivo characterization of three novel classes of VEGFR-2 (KDR) kinase inhibitors.* Proc Am Assoc Cancer Res 2002, 43: Abst 3676.

ABR-215050*

285383

4-Hydroxy-*N*-[4-(trifluoromethyl)phenyl]-5-methoxy-*N*,1-dimethyl-2-oxo-1,2-dihydroquinoline-3-carboxamide

ABR-5050



C20 H17 F3 N2 O4; Mol wt: 406.3583

ACTION – Antiangiogenic agent, active in an *in vivo* model of angiogenesis induced by vascular endothelial growth factor (VEGF) and against human prostate carcinoma xenografts in mice, where doses of 12.5 and 15 mg/kg p.o. b.i.d. produced respective 79 and 70% reductions in tumor growth, in the absence of toxicity.

SOURCE – Active Biotech.

REFERENCES

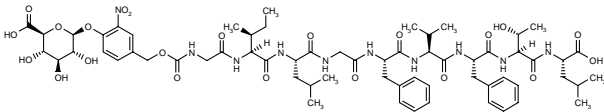
1. Björk, A. et al. (Active Biotech AB) *Quinoline derivs.* EP 1095021, WO 0003991.
2. Björk, A. et al. (Active Biotech AB) *Quinoline derivs.* US 6133285.
3. Pili, R. et al. *New quinoline-3-carboxamide derivatives inhibit VEGF-induced angiogenesis and human prostate carcinoma growth in vivo.* Proc Am Assoc Cancer Res 2002, 43: Abst 5363.

*Identified compound **285383** (see **285382**) Drug Data Rep 2000, 022(04): 0315.

OTHER ONCOLYTIC DRUGS

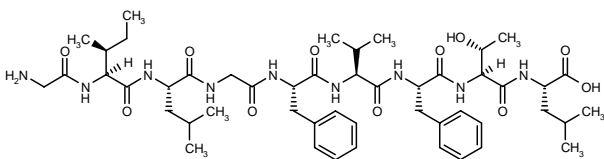
314974

N-[4-(β-D-Glucopyranuronosyloxy)-3-nitrobenzyloxy-carbonyl]-glycyl-L-isoleucyl-L-leucyl-glycyl-L-phenylalanyl-L-valyl-L-phenylalanyl-L-threonyl-L-leucine



C63 H88 N10 O22; Mol wt: 1337.4360

ACTION – Prodrug of the nonapeptide GILGFVFTL (MP58), a human leukocyte antigen (HLA-a2.1)-associated influenza peptide, activated by β-glucuronidase. Incubation of the prodrug with β-glucuronidase, as found in necrotic tumor sites, released free MP58, which binds to HLA-A2.1 on human T2 cells, thereby marking tumor cells for cytotoxic T-lymphocyte lysis. Another related prodrug is:



314975: C49 H75 N9 O11

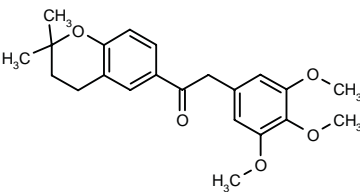
SOURCE – Wayne State University, Detroit, MI (US).

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1. Rawale, S. et al. *Synthesis and biological activity of the prodrug of class I major histocompatibility peptide GILGFVFTL activated by β-glucuronidase.* J Med Chem 2002, 45(4): 937.
2. Wei, W.-Z. et al. *Synthesis and anti-tumor activity of prodrug of HLA-A2.1 associated Flu peptide MP58 GILGFVVTL activated by β-glucurodinase.* Proc Am Assoc Cancer Res 2002, 43: Abst 3011.

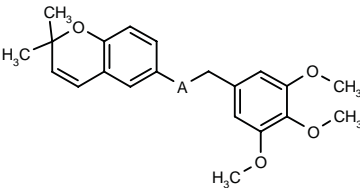
318960

1-(2,2-Dimethyl-3,4-dihydro-2*H*-1-benzopyran-6-yl)-2-(3,4,5-trimethoxyphenyl)ethanone



C22 H26 O5; Mol wt: 370.4424

ACTION – Antitumor agent that acts as an inhibitor of NADH-ubiquinone oxidoreductase, also known as NADH dehydrogenase (ubiquinone), with an IC₅₀ of 24 nM. Other exemplified compounds are:



Compound	A	Formula
318961	-S-	C ₂₁ H ₂₄ O ₄ S
318962	-COO-	C ₂₂ H ₂₄ O ₆
318978	-CO-	C ₂₂ H ₂₄ O ₅

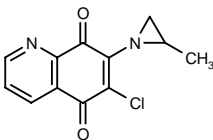
SOURCE – Scripps Research Institute, La Jolla, CA (US).

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1. Nicolaou, K.C. et al. (Scripps Research Institute) *Inhibitors of NADH:ubiquinone oxidoreductase.* WO 0220008.

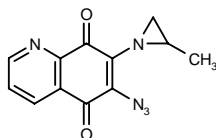
319533

6-Chloro-7-(2-methylaziridin-1-yl)-5,8-dihydroquinoline-5,8-dione



C12 H9 Cl N2 O2; Mol wt: 248.6681

ACTION – Antitumor agent shown to inhibit the proliferation of a panel of cancer cell lines with ED₅₀ values below 1 µg/ml. In acute toxicity tests, compound gave an LD₅₀ of 125 mg/kg i.v. in mice. Another exemplified aziridiny-substituted quinoline-5,8-dione derivative is:



319534: C₁₂ H₉ N₅ O₂

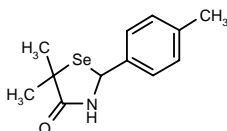
SOURCE – Korea Institute of Science and Technology, Seoul (KR).

REFERENCES

1. Kim, D.-J. et al. (Korea Institute of Science and Technology) *Aziridinyquinolinedione derivs. and process for their preparation*. WO 0234742.

320226

5,5-Dimethyl-2-(4-methylphenyl)-1,3-selenazolidin-4-one



C₁₂ H₁₅ N O Se; Mol wt: 268.2165

ACTION – Selenium-containing agent that inhibited tumor cell proliferation (IC₅₀ = 7.1 µM) and induced apoptosis in human ovarian cancer SK-OV-3 cells. Potentially useful for the treatment of gynecological tumors such as ovarian and breast cancer.

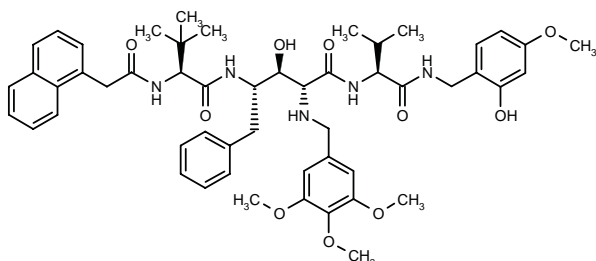
SOURCES – Gifu University, Gifu (JP); Ulsan University, Seoul (KR).

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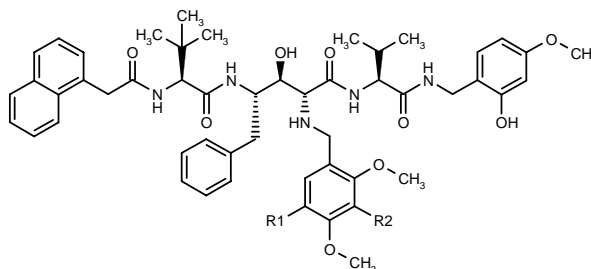
320233

N-[4(*S*)-[*N*-2-(1-Naphthyl)acetyl]-3-methyl-L-valylamino]-3(*R*)-hydroxy-2(*R*)-(3,4,5-trimethoxybenzylamino)-5-phenylpentanoyl]-L-valine 2-hydroxy-4-methoxybenzylamide



C₅₂ H₆₅ N₅ O₁₀; Mol wt: 920.1105

ACTION – Potent inhibitor of the chymotrypsin-like activity of the 20S proteasome (IC₅₀ = 7 nM) with high selectivity over trypsin-like and post-glutamyl-peptide hydrolytic activity of the proteasome (IC₅₀ > 20 µM). Potentially useful as a cytotoxic and antiproliferative agent. Other related compounds are:



Compound	R1	R2	Formula
320231	OMe	H	C ₅₂ H ₆₅ N ₅ O ₁₀
320232	H	OMe	C ₅₂ H ₆₅ N ₅ O ₁₀

SOURCE – Novartis.

REFERENCES

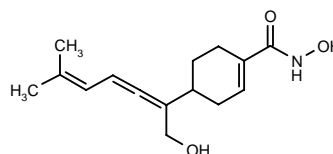
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2. Garcia-Echeverria, C. et al. *Structure-based optimization of non-covalent inhibitors of the chymotrypsin-like activity the 20S proteasome*. Proc Am Assoc Cancer Res 2002, 43: Abst 1023.

F-15603

319347

4-[1-(Hydroxymethyl)-5-methyl-1,2,4-hexatrienyl]-1-cyclohexene-1-carboxydroxamic acid



C₁₅ H₂₁ N O₃; Mol wt: 263.3349

ACTION – Antitumor compound isolated from cultures of *Stereum hirsutum* SANK 16000 (FERM BP-7200). Title compound is reported to induce apoptosis in *p53*-deficient cells, as demonstrated using *p53*-dysfunctional VA-13 cells (ED₅₀ = 0.91 µM vs. ED₅₀ > 37 µM for normal cells). In addition, F-15603 displayed cytotoxic activity comparable to doxorubicin and bleomycin when tested against a panel of tumor cell lines.

SOURCE – Sankyo.

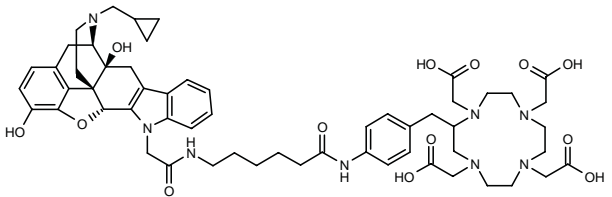
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NID-DOTA1

318753

2-[4-[6-[2-[17-(Cyclopropylmethyl)-6,7-didehydro-4,5α-epoxy-3,14β-dihydroxypyrrolo[2',3':6,7]morphinan-1'-yl]acetamido]hexanamido]benzyl]-1,4,7,10-tetrazacyclo-dodecan-1,4,7,10-tetraacetic acid



C57 H72 N8 O13; Mol wt: 1077.2390

ACTION – A representative compound within a series of conjugates comprising an opioid receptor-binding moiety and a therapeutically or diagnostically effective moiety selected from radionuclide chelators, fluorochromes, toxins, drugs, proteins, etc. Such a conjugate is expected to be useful for the treatment of cancer, particularly small cell lung cancer and other neuroendocrine cancers. NID-DOTA1 inhibited the binding of [³H]-naltrindole to opioid receptors in NG108-15 cells with an IC₅₀ of 12 nM.

SOURCE – NeoRx.

REFERENCES

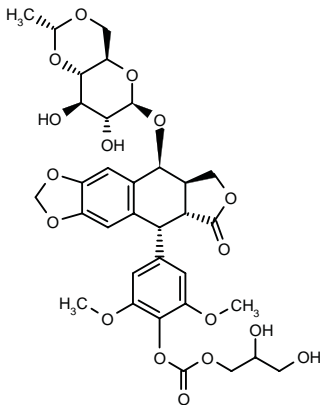
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ProVP-16II

318553

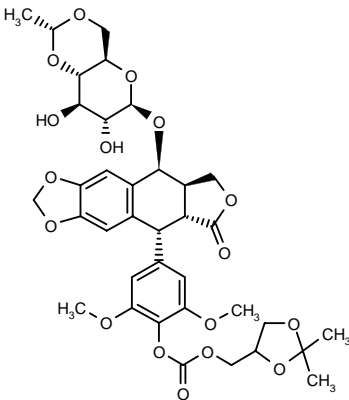
[5*R*-[5α,5aβ,8aα,9β(*R**)]]-5-[4-(2,3-Dihydroxypropoxycarbonyloxy)-3,5-dimethoxyphenyl]-9-(4,6-*O*-ethylidene-β-*D*-glucopyranosyloxy)-5,5a,6,8,8a,9-hexahydro-2*H*-furo[3',4':6,7]naphtho[2,3-*d*]-1,3-dioxol-6-one

4'-*O*-(2,3-Dihydroxypropoxycarbonyl)etoposide



C33 H38 O17; Mol wt: 706.6462

ACTION – Carbonate prodrug of etoposide that was stable for at least 1 week at physiological pH values and exhibited significantly higher *in vitro* cytotoxicity compared to the parent drug against a panel of multidrug-resistant cancer cell lines. The prodrug induced G₂/M phase synchronization and apoptosis in wild-type and resistant cells, whereas the parent compound only induced S phase delay; unlike etoposide, the prodrug did not inhibit topoisomerase II. *In vivo*, it exhibited a maximum tolerated dose 3-fold higher than that of etoposide and produced complete and long-lasting regression of established drug-resistant tumors. Another related prodrug is:



318552: C36 H42 O17

SOURCES – Humboldt-Universität zu Berlin, Berlin (DE); Tel Aviv University, Tel Aviv (IL).

REFERENCES

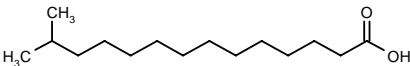
1. Schroeder, U. et al. *Novel carbonate prodrugs of etoposide are effective against multidrug resistance in vivo*. Proc Am Assoc Cancer Res 2002, 43: Abst 1043.
2. Wrasiklo, W. et al. *Synthesis, hydrolytic activation and cytotoxicity of etoposide prodrugs*. Bioorg Med Chem Lett 2002, 12(4): 557.

SUBTILOPENTADECANOIC ACID

286618

13-Methyltetradecanoic acid

13-MTD



C15 H30 O2; Mol wt: 242.4000

ACTION – Apoptosis inducer, a saturated branched-chain fatty acid component of a soy fermentation product widely used as a nutritional and therapeutic supplement in cancer therapy in China. Compound showed cytotoxic activity in several human cancer cell lines including breast cancer MCF7, leukemia K-562, prostate carcinoma DU 145 and colon carcinoma HCT 116 (ID₅₀ = 10-19 μg/ml). Compound induced apoptosis only in cancer cells via a mechanism linked to activation of the caspase pathway. *In vivo* anticancer efficacy was seen in several mouse models including murine cervical cancer U14, sarcoma 180, ascites liver cancer HAC, leukemia P388 tumors, as well as human prostate DU 145 and human hepatocellular carcinoma LCI-D35 xenografts. No systemic toxicity was seen after acute and chronic administration to rats (LD₅₀ > 5 g/kg i.g. and > 2 g/kg s.c.) and dogs; no influence on the immune system of normal or immunosuppressed mice was found, and compound appeared to alleviate the immunosuppression induced by chemotherapy.

SOURCE – Pentagenic.

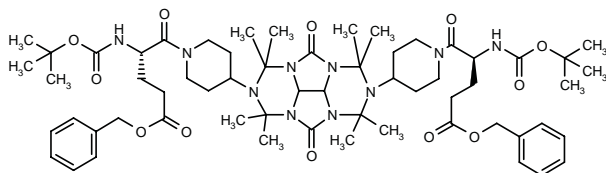
REFERENCES

1. Chen, X. et al. *Preclinical evaluation of 13-methyltetradecanoic acid*. Proc Am Assoc Cancer Res 2002, 43: Abst 394.
2. Yang, Z.H. et al. *Induction of apoptotic cell death and in vivo growth inhibition of human cancer cells by a saturated branched-chain fatty acid, 13-methyltetradecanoic acid*. Cancer Res 2000, 60(3): 505.
3. Zheng, J. et al. *13-Methyltetradecamic acid induces apoptosis in cancer cells but not in normal cells*. Proc Am Assoc Cancer Res 2001, 42: Abst 2378.

MODULATORS OF THE THERAPEUTIC ACTIVITY OF ANTINEOPLASTIC AGENTS

319149

2,6-[Bis-[1-[*O*-benzyl-*N*-(*tert*-butyloxycarbonyl)-L-glutamyl]piperidin-4-yl]perhydro-2,3a,4a,6,7a,8a-hexaazacyclopenta[*def*]fluorene-4,8-dione



C60 H88 N10 O12; Mol wt: 1141.4130

ACTION – Water-soluble compound with the ability to modulate multidrug resistance processes through interaction with ABC transporters of the MDR and MRP type. The compound demonstrated *in vitro* activity against the MDR1 and MRP1 transporters with IC₅₀ values in the low micromolar range.

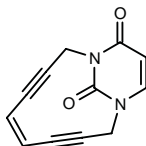
SOURCE – Solvo Biotechnology.

REFERENCES

1. Seprodi, J. et al. (Solvo Biotechnology, Inc.) *Soluble cpds. for the inhibition of multidrug resistance and pharmaceutical compsns. thereof*. WO 0220527.

319264

1,10-Diazabicyclo[8.3.1]tetradeca-5,12-diene-3,7-diyne-11,14-dione



C12 H8 N2 O2; Mol wt: 212.2072

ACTION – Nongenotoxic uracil-containing enediyne with cytotoxic activity against murine leukemia L1210 and P388, murine sarcoma S-180 and human leukemia CCRF-CEM cells (IC₅₀ = 0.23, 0.46, 1.55 and 0.38 μM, respectively) and no cytotoxicity against normal human embryonic lung cells up to 50 μM. Compound also exhibited a high synergistic effect in combination with doxorubicin and cytarabine.

SOURCES – Academia Sinica, Taipei (TW); University of Alberta, Edmonton, AB (CA).

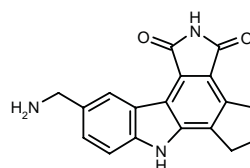
REFERENCES

1. Hakimelahi, G.H. et al. *A novel approach towards studying non-genotoxic enediyne as potential anticancer therapeutics*. Bioorg Med Chem 2002, 10(5): 1321.

CEP-6800

319811

10-(Aminomethyl)-4,5,6,7-tetrahydro-1*H*-cyclopenta[*a*]-pyrrolo[3,4-*c*]carbazole-1,3(2*H*)-dione



C18 H15 N3 O2; Mol wt: 305.3355

ACTION – Potent and selective PARP-1 (poly [ADP-ribose] polymerase, NAD⁺ ADP-ribosyltransferase) inhibitor (IC₅₀ = 17 and 300 nM in enzyme and cell-based assays, respectively) able to enhance the antitumor efficacy of irinotecan when used in combination (30 mg/kg s.c. and 10 mg/kg s.c., respectively) against human colon carcinoma HT-29 xenografts in mice. Compound alone had no antitumor activity in this model.

SOURCE – Cephalon.

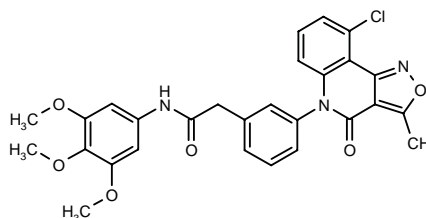
REFERENCES

1. Ator, M.A. et al. (Cephalon, Inc.) *Novel multicyclic cpds. and the use thereof*. WO 0185686.
2. Miknyoczki, S.J. et al. *Chemopotential of the antitumor efficacy of irinotecan in HT29 human colon carcinoma xenografts by the PARP inhibitor, CEP-6800*. Proc Am Assoc Cancer Res 2002, 43: Abst 3939.

LY-402913

282647

2-[3-(9-Chloro-3-methyl-4-oxo-4,5-dihydroisoxazolo-[4,3-*c*]quinolin-5-yl)phenyl]-*N*-(3,4,5-trimethoxyphenyl)-acetamide



C28 H24 Cl N3 O6; Mol wt: 533.9656

ACTION – Potent multidrug resistance protein (MRP1) inhibitor with approximately 22-fold selectivity over P-glycoprotein in HL60/Adr and HL60/Vinc cells. It was able to reverse drug resistance to MRP1 substrates such as doxorubicin in HeLa T5 cells (EC_{50} = 0.90 μ M) and ATP-dependent, MRP1-mediated LTC₄ uptake in MRP1-overexpressing HeLa T5 cells (EC_{50} = 1.8 μ M). *In vivo*, compound (10 mg/kg/day p.o. for 5 days) exhibited a synergistic effect in reducing tumor growth when given in combination with vincristine in the HeLa T5 xenograft model in mice.

SOURCE – Lilly.

REFERENCES

1. Ma, L. et al. *Functional characterization of canine MRP1 in HeLa and A2780 cells and its modulation by MRP1 modulator Ly402913*. Proc Am Assoc Cancer Res 2001, 42: Abst 5116.

2. Norman, B.H. et al. *Structure activity relationships of tricyclic isoxazoles, a novel class of selective MRP1 modulators*. Proc Am Assoc Cancer Res 2001, 42: Abst 5103.

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4. Paul, D.C. et al. *Selective modulation of MRP1 function by the tricyclic isoxazole, LY402913 and analogs of the natural product rufomycin*. Proc Am Assoc Cancer Res 2001, 42: Abst 5119.

5. Sun, H. et al. *Effect of LY-402913 on fluorescein transport in the central nervous system: An in vivo microdialysis study in freely-moving rats*. Annu Meet Am Assoc Pharm Sci (AAPS) (Nov 14-18, New Orleans) 1999, Abst.

6. Tabas, L. et al. *Effect of selective and novel MRP1 modulators on the transporter activity of MRP1*. Proc Am Assoc Cancer Res 2001, 42: Abst 5101.

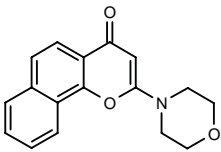
RADIATION THERAPY

NU-7026¹⁻⁵

311395

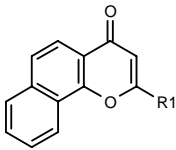
2-(4-Morpholinyl)-4*H*-benzo[*h*]-1-benzopyran-4-one

LY-293646

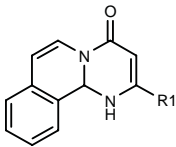


C17 H15 N O3; Mol wt: 281.3095

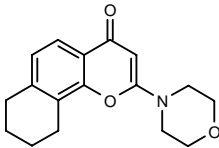
ACTION – Radiosensitizer, a DNA-dependent protein kinase inhibitor (IC_{50} = 0.5 μ M) proven to significantly sensitize HeLa cells to ionizing radiation and to inhibit the initial fast component of DNA double strand break repair in HeLa cells after radiation. Other related compounds are:



Compound	R1	Formula
NU-7163 [320267] ¹	2-Me-4-morpholinyl	C ₁₈ H ₁₇ NO ₃
NU-7052 [320268] ¹	4-thiomorpholinyl	C ₁₇ H ₁₅ NO ₂ S
NU-7165 [320390] ¹	cis-2,6-(Me)2-4-morpholinyl	C ₁₉ H ₁₉ NO ₃
NU-7180 [320392] ¹	2,2-(Me)2-4-morpholinyl	C ₁₉ H ₁₉ NO ₃
NU-7055 [320394] ¹	1-Pip	C ₁₈ H ₁₇ NO ₂



Compound	R1	Formula
NU-7079 [320266] ¹	4-morpholinyl	C ₁₆ H ₁₇ N ₃ O ₂
NU-7181 [320395] ¹	2-Et-4-morpholinyl	C ₁₈ H ₂₁ N ₃ O ₂
NU-7107 [320396] ¹	cis-2,6-(Me)2-4-morpholinyl	C ₁₈ H ₂₁ N ₃ O ₂
NU-7082 [320397] ¹	2,2-(Me)2-4-morpholinyl	C ₁₈ H ₂₁ N ₃ O ₂
NU-7124 [320398] ¹	4-thiomorpholinyl	C ₁₆ H ₁₇ N ₃ OS



NU-7046 [320265]¹: C17 H19 N O3

SOURCES – KuDOS Pharmaceuticals; University of Newcastle upon Tyne, Newcastle upon Tyne (GB).

REFERENCES

1. Griffin, R. et al. *Structure-based design of aurora kinase-2 inhibitors. Homology modeling and molecular dynamics docking simulation studies*. Proc Am Assoc Cancer Res 2002, 43: Abst 4210.

2. Veuger, S. et al. *Radiosensitization by novel inhibitors of PARP, PI and DNA-PK, NU7026, in vitro*. Br J Cancer 2001, 85(Suppl. 1): 37.

3. Veuger, S.J. et al. *Radiosensitization and modulation of DNA repair by novel inhibitors of PARP and DNA-PK in vitro*. Proc Am Assoc Cancer Res 2002, 43: Abst 4142.

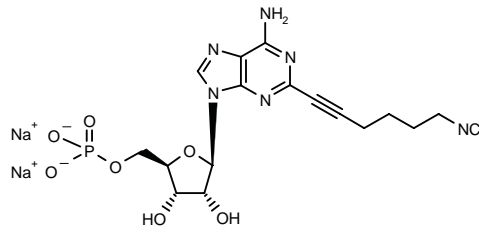
4. Veuger, S.J. et al. *Radiosensitization by the novel DNA-dependent protein kinase (DNA-PK) inhibitor, Nu7026, in vitro*. Proc Am Assoc Cancer Res 2001, 42: Abst 1092.

5. Vlahos, C.J. et al. *A specific inhibitor of phosphatidylinositol 3-kinase, 2-(4-morpholinyl)-8-phenyl-4*H*-1-benzopyran-4-one (LY294002)*. J Biol Chem 1994, 269(7): 5241.

OCULAR MEDICATIONS

319366

2-(6-Cyano-1-hexynyl)adenosine-5'-O-phosphate disodium salt



C17 H19 N6 Na2 O7 P; Mol wt: 496.3261

ACTION – A representative compound from a series of adenosine derivatives that act as intraocular pressure (IOP)-lowering agents and have potential in the treatment of glaucoma and ocular hypertension. Compound demonstrated *in vivo* IOP-lowering activity when topically administered to rabbits and was shown to be highly soluble in water.

SOURCES – Toa Eiyo; Yamasa Shoyu.

REFERENCES

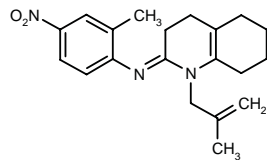
1. Konno, T. et al. (Toa Eiyo Ltd.;Yamasa Shoyu Co., Ltd.) *Adenosine derivs. and use thereof*. WO 0220539, WO 0220540.

METABOLIC DRUGS

TREATMENT OF BONE DISEASES

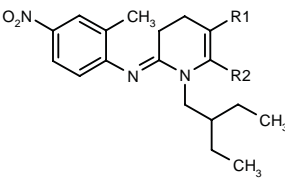
319148

N-(2-Methyl-4-nitrophenyl)-1-(2-methyl-2-propenyl)-1,2,3,4,5,6,7,8-octahydroquinolin-2-imine

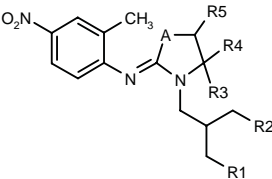


C20 H25 N3 O2; Mol wt: 339.4365

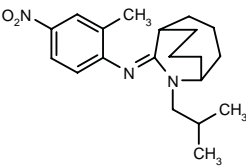
ACTION – A representative compound from a series of modulators of progesterone receptors, reportedly useful for the treatment of a broad range of progesterone-mediated conditions, particularly osteopenia, osteoporosis, bone fracture, for female contraception and in hormone replacement therapy.



Compound	R1	R2	Formula
319150	-(CH2)4-		C ₂₂ H ₃₁ N ₃ O ₂
319151	-CH=CHCH=CH-		C ₂₂ H ₂₇ N ₃ O ₂



Compound	R1=R2	R3	R4	R5	A	Isomer	Formula
319152	Me	H	-(CH2)4-	-CH2CH2-			C ₂₂ H ₃₃ N ₃ O ₂
319153	H	H	-(CH2)4-	-CH2CH2-	4aR*,8aS*		C ₂₀ H ₂₉ N ₃ O ₂
319155	H	-(CH2)4-	H	-CH2CH2-			C ₂₀ H ₂₉ N ₃ O ₂
319156	H	-(CH2)4-	H	-CH2-			C ₁₉ H ₂₇ N ₃ O ₂



319154: C20 H29 N3 O2

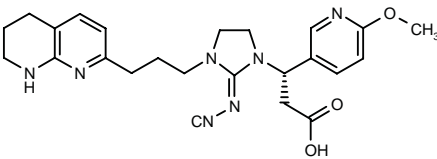
SOURCE – Bayer.

REFERENCES

1. Bullock, W.H. et al. (Bayer Corp.) *Cyclic and acyclic amidines and pharmaceutical compsns. containing them for use as progesterone receptor binding agents*. WO 0220526.

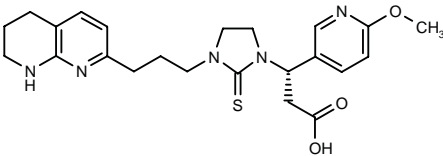
319286

3(S)-[2-(Cyanoimino)-3-[3-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)propyl]imidazolidin-1-yl]-3-(6-methoxypyridin-3-yl)propionic acid



C24 H29 N7 O3; Mol wt: 463.5391

ACTION – Agent with $\alpha_v\beta_3$ and/or $\alpha_v\beta_5$ integrin receptor-antagonist activity, potentially useful for the treatment of bone resorption, restenosis, angiogenesis, diabetic retinopathy, macular degeneration, inflammatory arthritis and cancer. Another specifically claimed compound is:

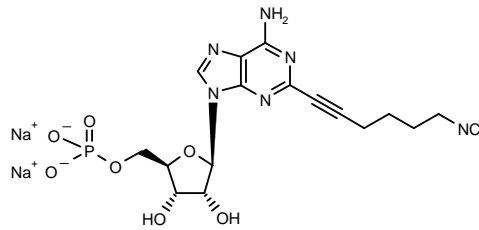


319287: C23 H29 N5 O3 S

OCULAR MEDICATIONS

319366

2-(6-Cyano-1-hexynyl)adenosine-5'-O-phosphate disodium salt



C17 H19 N6 Na2 O7 P; Mol wt: 496.3261

ACTION – A representative compound from a series of adenosine derivatives that act as intraocular pressure (IOP)-lowering agents and have potential in the treatment of glaucoma and ocular hypertension. Compound demonstrated *in vivo* IOP-lowering activity when topically administered to rabbits and was shown to be highly soluble in water.

SOURCES – Toa Eiyo; Yamasa Shoyu.

REFERENCES

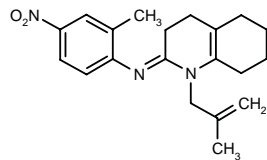
1. Konno, T. et al. (Toa Eiyo Ltd.;Yamasa Shoyu Co., Ltd.) *Adenosine derivs. and use thereof*. WO 0220539, WO 0220540.

METABOLIC DRUGS

TREATMENT OF BONE DISEASES

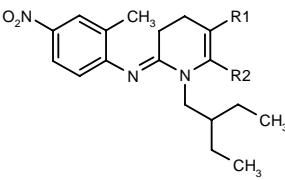
319148

N-(2-Methyl-4-nitrophenyl)-1-(2-methyl-2-propenyl)-1,2,3,4,5,6,7,8-octahydroquinolin-2-imine

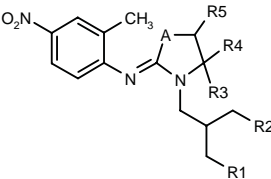


C20 H25 N3 O2; Mol wt: 339.4365

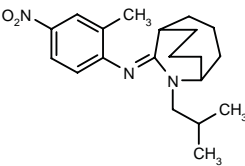
ACTION – A representative compound from a series of modulators of progesterone receptors, reportedly useful for the treatment of a broad range of progesterone-mediated conditions, particularly osteopenia, osteoporosis, bone fracture, for female contraception and in hormone replacement therapy.



Compound	R1	R2	Formula
319150	-(CH2)4-		C ₂₂ H ₃₁ N ₃ O ₂
319151	-CH=CHCH=CH-		C ₂₂ H ₂₇ N ₃ O ₂



Compound	R1=R2	R3	R4	R5	A	Isomer	Formula
319152	Me	H	-(CH2)4-	-CH2CH2-			C ₂₂ H ₃₃ N ₃ O ₂
319153	H	H	-(CH2)4-	-CH2CH2-	4aR*,8aS*		C ₂₀ H ₂₉ N ₃ O ₂
319155	H	-(CH2)4-	H	-CH2CH2-			C ₂₀ H ₂₉ N ₃ O ₂
319156	H	-(CH2)4-	H	-CH2-			C ₁₉ H ₂₇ N ₃ O ₂



319154: C20 H29 N3 O2

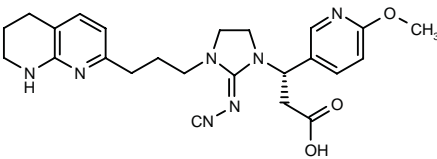
SOURCE – Bayer.

REFERENCES

1. Bullock, W.H. et al. (Bayer Corp.) *Cyclic and acyclic amidines and pharmaceutical compsns. containing them for use as progesterone receptor binding agents*. WO 0220526.

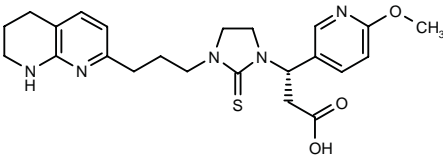
319286

3(S)-[2-(Cyanoimino)-3-[3-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)propyl]imidazolidin-1-yl]-3-(6-methoxypyridin-3-yl)propionic acid



C24 H29 N7 O3; Mol wt: 463.5391

ACTION – Agent with $\alpha_v\beta_3$ and/or $\alpha_v\beta_5$ integrin receptor-antagonist activity, potentially useful for the treatment of bone resorption, restenosis, angiogenesis, diabetic retinopathy, macular degeneration, inflammatory arthritis and cancer. Another specifically claimed compound is:



319287: C23 H29 N5 O3 S

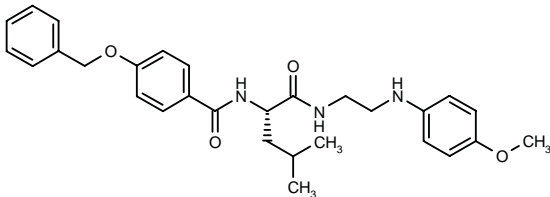
SOURCE – Merck & Co.

REFERENCES

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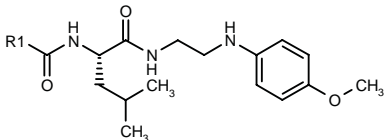
319529

N²-[4-(Benzyloxy)benzoyl]-N¹-[2-(4-methoxyphenyl)amino]ethyl-L-leucinamide



C29 H35 N3 O4; Mol wt: 489.6125

ACTION – Potent, noncovalent cathepsin K inhibitor (IC₅₀ < 0.003 μM; K_i = 0.015 μM against rabbit enzyme) with high selectivity for human cathepsin K over human cathepsin S and L (IC₅₀ = 0.006, 9.5 and > 10 μM, respectively). Potentially useful for the treatment of diseases characterized by excessive bone loss such as osteoporosis. Other related compounds are:



Compound	R1	Formula
319530	5-i-Pr-2-Pyr	C ₂₄ H ₃₄ N ₄ O ₃
319531	1-(2-Cl-Ph)-1,2,4-triazol-3-yl	C ₂₄ H ₂₉ ClN ₆ O ₃

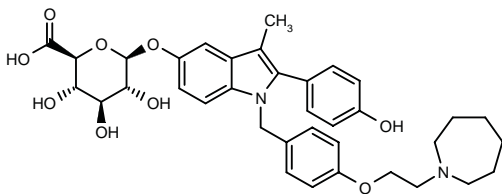
SOURCE – Novartis.

REFERENCES

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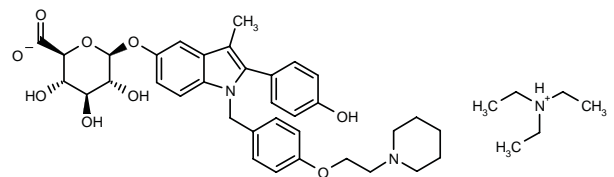
319581

1-O-[2-(4-Hydroxyphenyl)-3-methyl-1-[4-[2-(perhydroazepin-1-yl)ethoxy]benzyl]-1H-indol-5-yl]-β-D-glucopyranosiduronic acid

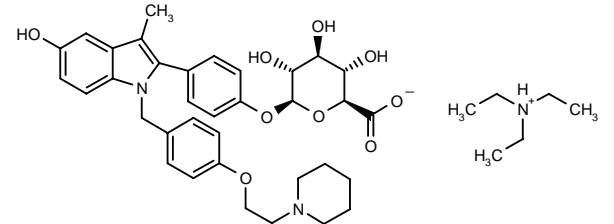


C36 H42 N2 O9; Mol wt: 646.7328

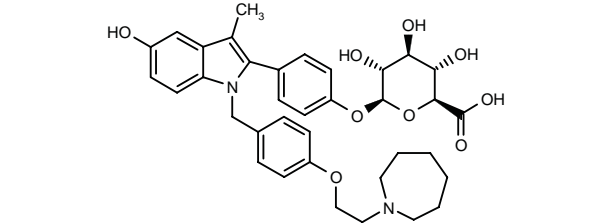
ACTION – Tissue-selective estrogenic agent reported to act as an estrogen agonist in certain tissues, thus having potential for the treatment of osteoporosis, prostatic hypertrophy, vaginal and skin atrophy, acne, cardiovascular disease, contraception and postmenopausal disorders, while exhibiting estrogen-antagonist activity in other tissues, therefore being useful for the treatment of male pattern baldness, dysfunctional uterine bleeding, hormone-related cancer, endometriosis, Alzheimer's disease, etc. Compound displayed antagonist activity (IC₅₀ = 210 nM) when tested against estrogen receptors expressed in human mammary-derived MCF7 cells. Other exemplified compounds are:



319582:C35 H39 N2 O9 . C6 H16 N



319583: C35 H39 N2 O9 . C6 H16 N



319584: C36 H42 N2 O9

SOURCE – Wyeth.

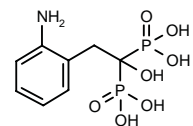
REFERENCES

1. Miller, C.P. et al. (American Home Products Corporation) *Glucopyranosides conjugates of 2-(4-hydroxy-phenyl)-3-methyl-1-[4-(2-amin-1-yl-ethoxy)-benzyl]-1H-indol-5-ols*. US 6380166.

NE-21650

304481

2-(2-Aminophenyl)-1-hydroxyethane-1,1-diphosphonic acid



C8 H13 N O7 P2; Mol wt: 297.1387

ACTION – Nitrogen-containing bisphosphonate that inhibits recombinant human farnesyl diphosphate synthase (FPP synthetase, geranyltranstransferase) and the related enzyme isopentenyl-diphosphate δ -isomerase (IPP isomerase) with respective IC₅₀ values of 58 nM and 70 μ M; the reference compound alendronate inhibited human FPP synthase with comparable potency (IC₅₀ = 53 nM) but was inactive against human IPP isomerase. Compound also inhibited protein prenylation in macrophages and rabbit osteoclasts. In a rabbit osteoclast bone resorption assay, it was slightly but significantly more effective than alendronate in inhibiting resorption at concentrations of 10 μ M or more. Potentially useful for the treatment of bone resorption in osteoporosis, metastatic bone disease and hypercalcemia.

SOURCE – Procter & Gamble.

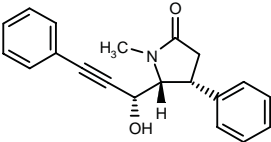
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1. Thompson, K. et al. *Identification of a bisphosphonate that inhibits isopentenyl diphosphate isomerase and farnesyl diphosphate synthase*. Biochem Biophys Res Commun 2002, 290(2): 869.

2. Thompson, K. et al. *Identification of a bisphosphonate which inhibit FPP synthase and IPP isomerase*. Bone 2001, 28(5, Suppl.): Abst SC1 W.

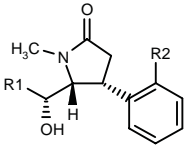
319203

(\pm)-5(*R*^{*})-[1(*R*^{*})-Hydroxy-3-phenyl-2-propynyl]-1-methyl-4(*R*^{*})-phenylpyrrolidin-2-one

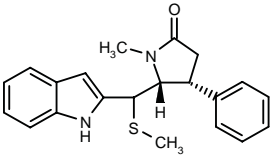


C20 H19 N O2; Mol wt: 305.3751

ACTION – An inhibitor of 17 β -hydroxysteroid dehydrogenase type 2 (17 β -HSD-2; IC₅₀ < 500 nM), potentially useful for the treatment of osteoporosis, osteopenia, ovarian cancer, breast cancer, endometrial cancer, endometriosis, prostate cancer, acne, androgen-dependent hair loss, type 2 diabetes and hypercholesterolemia. Other exemplified 4-phenylpyrrolidinone derivatives are:



Compound	R1	R2	Formula
319206	5-ethynyl-2-thienyl	H	C ₁₈ H ₁₇ NO ₂ S
319207	5-(4-thiomorpholinyl-SO ₂)-2-thienyl	H	C ₂₀ H ₂₄ N ₂ O ₄ S ₃
319208	5-(3-NH ₂ -Ph)-2-thienyl	H	C ₂₂ H ₂₂ N ₂ O ₂ S
319210	3,4-(Cl) ₂ -Ph	H	C ₁₈ H ₁₇ Cl ₂ NO ₂
319211	4-F-Ph-ethynyl	H	C ₂₀ H ₁₈ FNO ₂
319212	5-(2-thienyl)-2-thienyl	F	C ₂₀ H ₁₈ FNO ₂ S ₂



319204: C21 H22 N2 O S

SOURCE – Bayer.

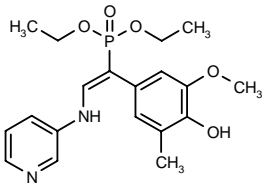
REFERENCES

1. Wood, J.E. et al. (Bayer Corp.) *17- β -Hydroxysteroid dehydrogenase-II inhibitors*. WO 0226706.

TREATMENT OF LIPOPROTEIN DISORDERS

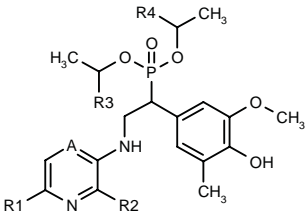
318595

(*E*)-1-(4-Hydroxy-3-methoxy-5-methylphenyl)-2-(pyridin-3-ylamino)vinylphosphonic acid diethyl ester

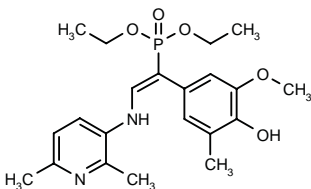


C19 H25 N2 O5 P; Mol wt: 392.3895

ACTION – Agent with the ability to lower plasma levels of apolipoproteins A and B (apo A and apo B) and cholesterol. It demonstrated *in vitro* apo A-lowering activity in cynomolgus monkey hepatocytes at 20 μ M. *In vivo* plasma apo A,- apo B- and cholesterol-lowering activity was also seen following oral administration to monkeys at 50 mg/kg/day for 2 weeks. Potentially useful for the treatment of atherosclerosis, thrombosis, restenosis and hypercholesterolemia. Other exemplified phosphonates are:



Compound	R1	R2	R3=R4	A	Formula
318598	Me	Me	H	CH	C ₂₁ H ₃₁ N ₂ O ₅ P
318600	Me	Me	Me	CH	C ₂₃ H ₃₅ N ₂ O ₅ P
318601	Me	H	H	CH	C ₂₀ H ₂₉ N ₂ O ₅ P
318603	H	H	H	N	C ₁₈ H ₂₆ N ₃ O ₅ P

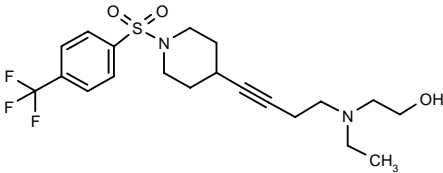


318596: C21 H29 N2 O5 P

SOURCE – Ilex Oncology.

REFERENCES

1. Phan, H.T. et al. (Ilex Oncology Research S.A.) *α-Substd. β-aminoethyl phosphonates*. WO 0226752.



319059: C20 H27 F3 N2 O3 S

SOURCE – Roche.

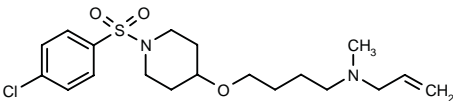
REFERENCES

1. Ackermann, J. et al. (F. Hoffmann-La Roche AG) *Novel piperidine derivs*. WO 0220483.

319051

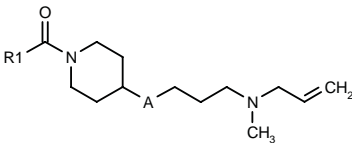
N-[4-[1-(4-Chlorophenylsulfonyl)piperidin-4-yloxy]butyl]-*N*-methyl-2-propen-1-amine

N-Allyl-*N*-[4-[1-(4-chlorophenylsulfonyl)piperidin-4-yloxy]butyl]-*N*-methylamine

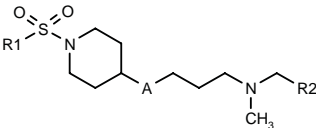


C19 H29 Cl N2 O3 S; Mol wt: 400.9681

ACTION – An inhibitor of 2,3-epoxysqualene–lanosterol cyclase (lanosterol synthase) with potential in the treatment of hypercholesterolemia, hyperlipidemia, arteriosclerosis, vascular diseases, fungal and parasitic infections, gallstones, cancer and other proliferative disorders, impaired glucose tolerance and diabetes. Other exemplified piperidine derivatives include the following:



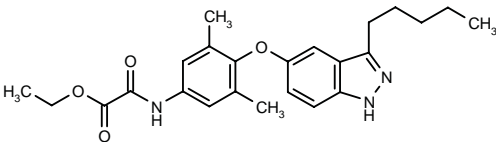
Compound	R1	A	Formula
319052	i-BuO	-O(CH2)3-	C ₂₀ H ₃₈ N ₂ O ₃
319053	4-Cl-Ph	-CH2CH2OCH2-	C ₂₂ H ₃₃ ClN ₂ O ₂
319054	4-Cl-Ph	-CH2O-	C ₂₀ H ₂₉ ClN ₂ O ₂



Compound	R1	R2	R3	Formula
319055	NHBu	vinyl	-O(CH2)3-	C ₁₉ H ₃₉ N ₃ O ₃ S
319056	4-Br-PhNH	vinyl	-O(CH2)3-	C ₂₁ H ₃₄ BrN ₃ O ₃ S
319057	2,5-(F)2-PhNH	vinyl	-O(CH2)3-	C ₂₁ H ₃₃ F ₂ N ₃ O ₃ S
319060	4-CF3-Ph	Et	-CH2-	C ₂₀ H ₃₁ F ₃ N ₂ O ₂ S

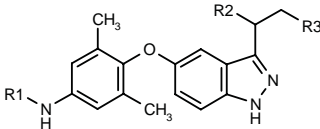
319358

N-[3,5-Dimethyl-4-(3-pentyl-1 *H*-indazol-5-yloxy)phenyl]-oxamic acid ethyl ester



C24 H29 N3 O4; Mol wt: 423.5101

ACTION – A thyroid hormone agonist, potentially useful for the treatment of arteriosclerosis and hypercholesterolemia. Compound demonstrated a thyroid hormone-like profile, inducing luciferase activity in HepG2 cells transfected with the luciferase gene under the control of a thyroid hormone-regulated promoter (EC₅₀ = 10 nM). Other exemplified 1*H*-indazole derivatives are:



Compound	R1	R2	R3	Formula
319360	H	H	Me	C ₁₈ H ₂₁ N ₃ O
319361	COCO2Et	Me	H	C ₂₂ H ₂₆ N ₃ O ₄
319363	COCO2H	H	Pr	C ₂₂ H ₂₆ N ₃ O ₄
319364	CH2CO2Et	H	Pr	C ₂₄ H ₃₁ N ₃ O ₃
319365	COCH2CO2Me	H	Pr	C ₂₄ H ₂₉ N ₃ O ₄

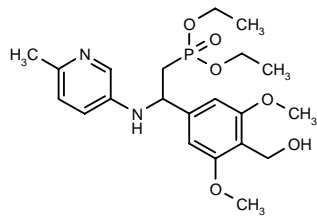
SOURCE – Bayer.

REFERENCES

1. Woltering, M. et al. (Bayer AG) *Indazoles having an action similar to that of a thyroid hormone, method for the production thereof, and their use in medicaments*. DE 10046029, WO 0222586.

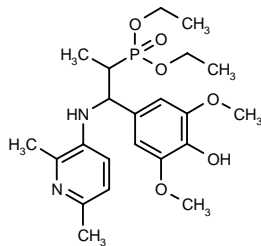
319568

2-[4-(Hydroxymethyl)-3,5-dimethoxyphenyl]-2-(6-methylpyridin-3-ylamino)ethylphosphonic acid diethyl ester



C21 H31 N2 O6 P; Mol wt: 438.4579

ACTION – Agent with the ability to lower plasma levels of apolipoproteins A and B (apo A and apo B) and cholesterol, shown to decrease apo A secretion in cyno-molgus monkey hepatocytes at 20 µM. *In vivo*, oral administration of compound at 25 mg/kg/day for 4 weeks resulted in measurable decreases in the plasma levels of apo A, apo B and total cholesterol. Potentially useful for the treatment of atherosclerosis, hypercholesterolemia and postangioplasty restenosis. Another exemplified phosphonate is:



319569: C22 H33 N2 O6 P

SOURCE – Ilex Oncology.

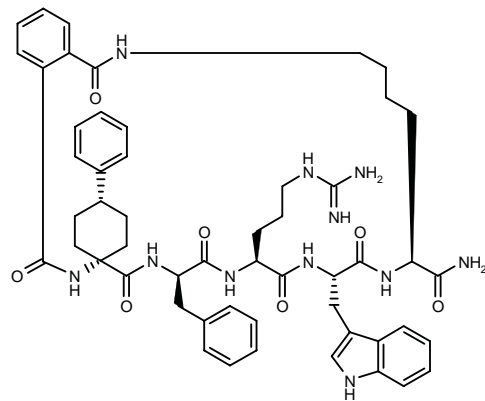
REFERENCES

1. Phan, H.T. et al. (Ilex Oncology Research S.A.) *β*-Substd. *β*-aminoethyl phosphonates. WO 0234756.

TREATMENT OF OBESITY
AND NUTRITIONAL DISORDERS

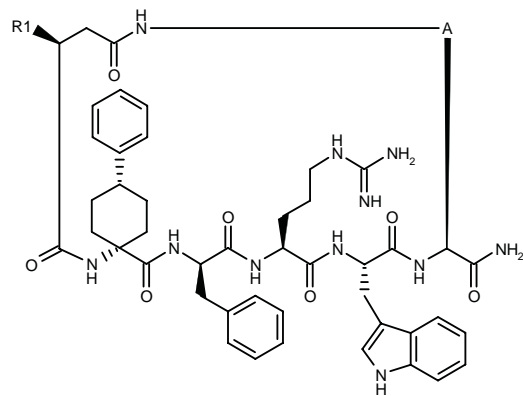
318300

(6*R*,9*S*,12*S*,15*S*)-6-Benzyl-9-(3-guanidinopropyl)-12-(1*H*-indol-3-ylmethyl)-1,4,7,10,13,21-hexaoxo-4'-phenyl-1,2,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21-icosahydrospiro[2,5,8,11,14,20-benzohexa-azacyclotricosine-3,1'-cyclohexane]-15-carboxamide



C53 H63 N11 O7; Mol wt: 966.1507

ACTION – Selective melanocortin MC₄ receptor agonist that gave an EC₅₀ of 3.1 nM at MC₄ receptors and exhibited 700-fold selectivity over MC₁ receptors. Potentially useful for the treatment of obesity. Other exemplified cyclic peptides are:



Compound	R1	A	Formula
318301	H	-(CH2)4-	C ₄₉ H ₆₃ N ₁₁ O ₇
318302	NHCOBu	-CH2-	C ₅₁ H ₆₆ N ₁₂ O ₈
318303	NHAc	-CH2-	C ₄₈ H ₆₀ N ₁₂ O ₈

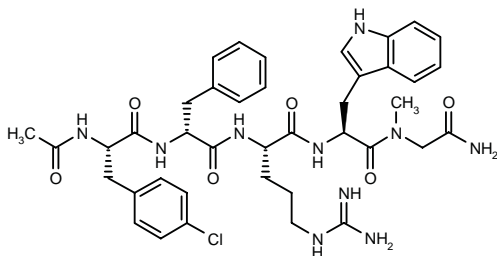
SOURCE – Roche.

REFERENCES

1. Chen, L. et al. (F. Hoffmann-La Roche AG) *Selective cyclic peptides*. WO 0218437.

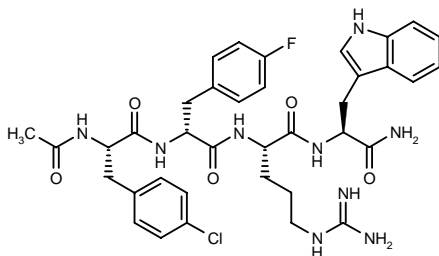
319098

N-Acetyl-4-chloro-L-phenylalanyl-D-phenylalanyl-L-arginyl-L-tryptophyl-*N*²-methylglycinamide



C40 H49 Cl N10 O6; Mol wt: 801.3441

ACTION – Peptidomimetic compound with high affinity for melanocortin MC₃ and/or MC₄ receptors and selectivity over the MC₁ receptor subtype. It was shown to induce weight loss and reduced adiposity when administered to an obese woman at 0.1 mg/kg s.c. over a 6-month period. Potentially useful for the treatment of obesity, anorexia and cachexia, as well as insulin resistance, glucose intolerance, type 2 diabetes, coronary artery disease, hypertension, dyslipidemia, cancer, menstrual irregularities, hirsutism, infertility, gallbladder disease, restrictive lung disease, sleep apnea, gout, osteoarthritis and thromboembolic disorders. Another related compound is:



319099: C37 H43 Cl F N9 O5

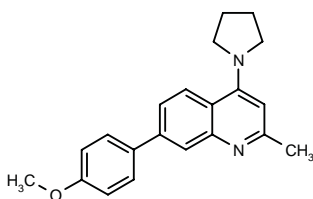
SOURCE – Procter & Gamble.

REFERENCES

1. Ebetino, F.H. et al. (The Procter & Gamble Co.) *Melanocortin receptor ligands*. WO 0226774.

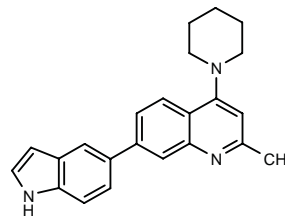
319351

7-(4-Methoxyphenyl)-2-methyl-4-(1-pyrrolidinyl)quinoline



C21 H22 N2 O; Mol wt: 318.4178

ACTION – Neuropeptide Y (NPY) Y₅ receptor antagonist that gave an IC₅₀ of 0.06 μM when tested against Y₅ receptors expressed in HEK293 cells. Potentially useful for the treatment of obesity and other NPY-mediated disorders such as arthritis, cardiovascular diseases, diabetes and renal failure. Another compound within this series of quinoline and quinazoline derivatives is:



319352: C23 H23 N3

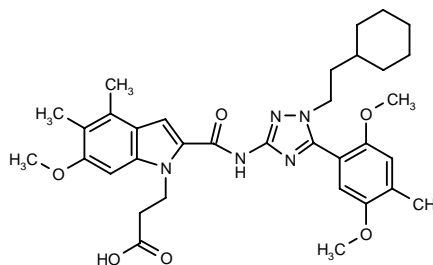
SOURCE – Roche.

REFERENCES

1. Breu, V. et al. (F. Hoffmann-La Roche AG) *Quinoline and quinazoline derivs*. US 2002052356, WO 0220488.

319532

3-[2-[*N*-(1-(2-Cyclohexylethyl)-5-(2,5-dimethoxy-4-methylphenyl)-1*H*-1,2,4-triazol-3-yl)]carbamoyl]-6-methoxy-4,5-dimethyl-1*H*-indol-1-yl]propionic acid



C34 H43 N5 O6; Mol wt: 617.7427

ACTION – A specifically claimed compound from a series of triazole derivatives that acts as a selective cholecystokinin CCK₁ (CCK_A) receptor agonist, potentially useful for the treatment of obesity.

SOURCE – Sanofi-Synthélabo.

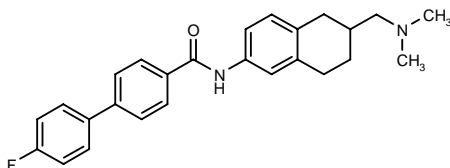
REFERENCES

1. Bignon, E. et al. (Sanofi-Synthélabo) *Triazole derivs. and pharmaceutical compsns. comprising them*. WO 0234743.

T-226296

320449

(-)-N-[6-(Dimethylaminomethyl)-5,6,7,8-tetrahydronaphthalen-2-yl]-4'-fluorobiphenyl-4-carboxamide



C26 H27 F N2 O; Mol wt: 402.5103

ACTION – Orally active melanin-concentrating hormone (MCH) receptor antagonist with high affinity for the SLC-1 subtype of MCH receptors ($IC_{50} = 5.5$ and 8.6 nM, for human and rat receptors, respectively) and high selectivity over the SLT subtype of MCH receptors and a range of other receptors, ion channels and transporters. Functional assays using human SLC-1 receptors expressed in CHO cells showed that compound inhibited the MCH-induced release of arachidonic acid ($pA_2 = 7.5$), reversed the MCH-induced inhibition of forskolin-stimulated cAMP accumulation ($IC_{50} = 160$ nM) and inhibited the MCH-induced increase in intracellular Ca^{2+} levels (IC_{50} approximately 100 nM). In rats, compound (30 mg/kg p.o.) produced almost complete suppression of food intake induced by intracerebroventricular administration of MCH. Potentially useful as a pharmacological tool for elucidating the physiological and pathophysiological roles of the MCH receptor, as well as for the treatment of obesity.

SOURCE – Takeda.

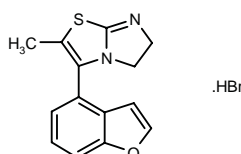
REFERENCES

1. Kato, K. et al. (Takeda Chemical Industries, Ltd.) *Melanin concentrating hormone antagonist*. JP 2002003370, WO 0121577.
2. Takekawa, S. et al. *T-226296: A novel, orally active and selective melanin-concentrating hormone receptor antagonist*. Eur J Pharmacol 2002, 438(3): 129.

TREATMENT OF POISONING, DRUG ABUSE AND DEPENDENCY

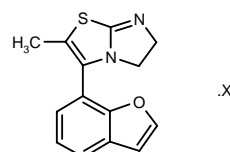
318554

3-(1-Benzofuran-4-yl)-2-methyl-5,6-dihydroimidazo[2,1-b]thiazole hydrobromide



C14 H12 N2 O S . HBr; Mol wt: 337.2397

ACTION – 5-HT_{1A} receptor ligand ($K_i = 52$ nM) that is also able to inhibit neuronal reuptake of 5-HT (88% at $1 \mu M$) and noradrenaline ($K_i = 7.7$ nM) in rat cortical preparations. In addition, this compound displayed little activity at muscarinic receptors related to undesirable side effects. Potentially useful for reducing craving and weight gain after smoking cessation and for the treatment of obesity. Other applications include depression, anxiety, schizophrenia, tardive dyskinesia, drug abuse, Alzheimer's disease, obsessive-compulsive disorder, panic, eating disorders, type 2 diabetes, hyperglycemia, hyperlipidemia, stress, seizures, stroke, brain trauma and cerebral ischemia, and also metabolic disorders such as sexual dysfunction, sleep apnea, urinary incontinence, pain, osteoarthritis, gout and pulmonary hypertension. Other exemplified compounds are:



Compound	X	Formula
318555	HBr	$C_{14}H_{12}N_2OS \cdot HBr$
318556	HCl	$C_{14}H_{12}N_2OS \cdot HCl$

SOURCE – Abbott.

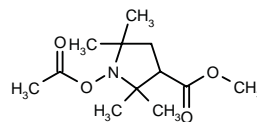
REFERENCES

1. Brough, P. et al. (Knoll GmbH) *Dihydroimidazo[2,1-b]thiazole and dihydro-5H-thiazolo[3,2-a]pyrimidine derivatives with 5-HT receptor affinity*. WO 0226747.

DIAGNOSTIC AGENTS

318373

1-Acetoxy-2,2,5,5-tetramethylpyrrolidine-3-carboxylic acid methyl ester



C12 H21 N O4; Mol wt: 243.3009

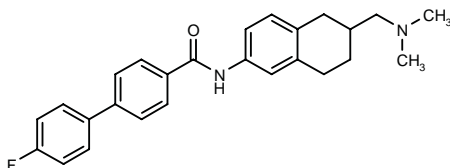
ACTION – Spin label generator for electron paramagnetic resonance (EPR) brain imaging, a lipophilic agent that easily penetrates the blood-brain barrier, where it is retained for a clinically relevant period of time. In brain, it was deacetylated and oxidized by intracellular oxidants to an EPR-detectable nitroxide.

SOURCE – National Institutes of Health, Bethesda, MD

T-226296

320449

(-)-N-[6-(Dimethylaminomethyl)-5,6,7,8-tetrahydronaphthalen-2-yl]-4'-fluorobiphenyl-4-carboxamide



C26 H27 F N2 O; Mol wt: 402.5103

ACTION – Orally active melanin-concentrating hormone (MCH) receptor antagonist with high affinity for the SLC-1 subtype of MCH receptors ($IC_{50} = 5.5$ and 8.6 nM, for human and rat receptors, respectively) and high selectivity over the SLT subtype of MCH receptors and a range of other receptors, ion channels and transporters. Functional assays using human SLC-1 receptors expressed in CHO cells showed that compound inhibited the MCH-induced release of arachidonic acid ($pA_2 = 7.5$), reversed the MCH-induced inhibition of forskolin-stimulated cAMP accumulation ($IC_{50} = 160$ nM) and inhibited the MCH-induced increase in intracellular Ca^{2+} levels (IC_{50} approximately 100 nM). In rats, compound (30 mg/kg p.o.) produced almost complete suppression of food intake induced by intracerebroventricular administration of MCH. Potentially useful as a pharmacological tool for elucidating the physiological and pathophysiological roles of the MCH receptor, as well as for the treatment of obesity.

SOURCE – Takeda.

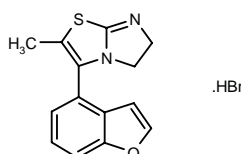
REFERENCES

1. Kato, K. et al. (Takeda Chemical Industries, Ltd.) *Melanin concentrating hormone antagonist*. JP 2002003370, WO 0121577.
2. Takekawa, S. et al. *T-226296: A novel, orally active and selective melanin-concentrating hormone receptor antagonist*. Eur J Pharmacol 2002, 438(3): 129.

TREATMENT OF POISONING, DRUG ABUSE AND DEPENDENCY

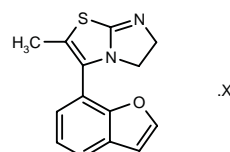
318554

3-(1-Benzofuran-4-yl)-2-methyl-5,6-dihydroimidazo[2,1-b]thiazole hydrobromide



C14 H12 N2 O S . HBr; Mol wt: 337.2397

ACTION – 5-HT_{1A} receptor ligand ($K_i = 52$ nM) that is also able to inhibit neuronal reuptake of 5-HT (88% at $1 \mu M$) and noradrenaline ($K_i = 7.7$ nM) in rat cortical preparations. In addition, this compound displayed little activity at muscarinic receptors related to undesirable side effects. Potentially useful for reducing craving and weight gain after smoking cessation and for the treatment of obesity. Other applications include depression, anxiety, schizophrenia, tardive dyskinesia, drug abuse, Alzheimer's disease, obsessive-compulsive disorder, panic, eating disorders, type 2 diabetes, hyperglycemia, hyperlipidemia, stress, seizures, stroke, brain trauma and cerebral ischemia, and also metabolic disorders such as sexual dysfunction, sleep apnea, urinary incontinence, pain, osteoarthritis, gout and pulmonary hypertension. Other exemplified compounds are:



Compound	X	Formula
318555	HBr	$C_{14}H_{12}N_2OS \cdot HBr$
318556	HCl	$C_{14}H_{12}N_2OS \cdot HCl$

SOURCE – Abbott.

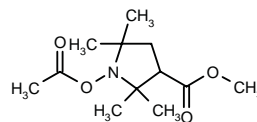
REFERENCES

1. Brough, P. et al. (Knoll GmbH) *Dihydroimidazo[2,1-b]thiazole and dihydro-5H-thiazolo[3,2-a]pyrimidine derivatives with 5-HT receptor affinity*. WO 0226747.

DIAGNOSTIC AGENTS

318373

1-Acetoxy-2,2,5,5-tetramethylpyrrolidine-3-carboxylic acid methyl ester



C12 H21 N O4; Mol wt: 243.3009

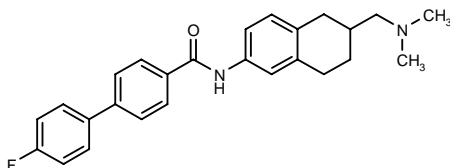
ACTION – Spin label generator for electron paramagnetic resonance (EPR) brain imaging, a lipophilic agent that easily penetrates the blood-brain barrier, where it is retained for a clinically relevant period of time. In brain, it was deacetylated and oxidized by intracellular oxidants to an EPR-detectable nitroxide.

SOURCE – National Institutes of Health, Bethesda, MD

T-226296

320449

(-)-N-[6-(Dimethylaminomethyl)-5,6,7,8-tetrahydronaphthalen-2-yl]-4'-fluorobiphenyl-4-carboxamide



C26 H27 F N2 O; Mol wt: 402.5103

ACTION – Orally active melanin-concentrating hormone (MCH) receptor antagonist with high affinity for the SLC-1 subtype of MCH receptors ($IC_{50} = 5.5$ and 8.6 nM, for human and rat receptors, respectively) and high selectivity over the SLT subtype of MCH receptors and a range of other receptors, ion channels and transporters. Functional assays using human SLC-1 receptors expressed in CHO cells showed that compound inhibited the MCH-induced release of arachidonic acid ($pA_2 = 7.5$), reversed the MCH-induced inhibition of forskolin-stimulated cAMP accumulation ($IC_{50} = 160$ nM) and inhibited the MCH-induced increase in intracellular Ca^{2+} levels (IC_{50} approximately 100 nM). In rats, compound (30 mg/kg p.o.) produced almost complete suppression of food intake induced by intracerebroventricular administration of MCH. Potentially useful as a pharmacological tool for elucidating the physiological and pathophysiological roles of the MCH receptor, as well as for the treatment of obesity.

SOURCE – Takeda.

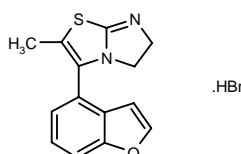
REFERENCES

1. Kato, K. et al. (Takeda Chemical Industries, Ltd.) *Melanin concentrating hormone antagonist*. JP 2002003370, WO 0121577.
2. Takekawa, S. et al. *T-226296: A novel, orally active and selective melanin-concentrating hormone receptor antagonist*. Eur J Pharmacol 2002, 438(3): 129.

TREATMENT OF POISONING, DRUG ABUSE AND DEPENDENCY

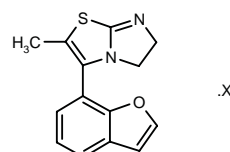
318554

3-(1-Benzofuran-4-yl)-2-methyl-5,6-dihydroimidazo[2,1-b]thiazole hydrobromide



C14 H12 N2 O S . HBr; Mol wt: 337.2397

ACTION – 5-HT_{1A} receptor ligand ($K_i = 52$ nM) that is also able to inhibit neuronal reuptake of 5-HT (88% at $1 \mu M$) and noradrenaline ($K_i = 7.7$ nM) in rat cortical preparations. In addition, this compound displayed little activity at muscarinic receptors related to undesirable side effects. Potentially useful for reducing craving and weight gain after smoking cessation and for the treatment of obesity. Other applications include depression, anxiety, schizophrenia, tardive dyskinesia, drug abuse, Alzheimer's disease, obsessive-compulsive disorder, panic, eating disorders, type 2 diabetes, hyperglycemia, hyperlipidemia, stress, seizures, stroke, brain trauma and cerebral ischemia, and also metabolic disorders such as sexual dysfunction, sleep apnea, urinary incontinence, pain, osteoarthritis, gout and pulmonary hypertension. Other exemplified compounds are:



Compound	X	Formula
318555	HBr	$C_{14}H_{12}N_2OS \cdot HBr$
318556	HCl	$C_{14}H_{12}N_2OS \cdot HCl$

SOURCE – Abbott.

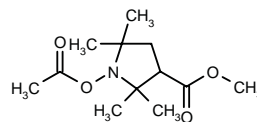
REFERENCES

1. Brough, P. et al. (Knoll GmbH) *Dihydroimidazo[2,1-b]thiazole and dihydro-5H-thiazolo[3,2-a]pyrimidine derivatives with 5-HT receptor affinity*. WO 0226747.

DIAGNOSTIC AGENTS

318373

1-Acetoxy-2,2,5,5-tetramethylpyrrolidine-3-carboxylic acid methyl ester



C12 H21 N O4; Mol wt: 243.3009

ACTION – Spin label generator for electron paramagnetic resonance (EPR) brain imaging, a lipophilic agent that easily penetrates the blood-brain barrier, where it is retained for a clinically relevant period of time. In brain, it was deacetylated and oxidized by intracellular oxidants to an EPR-detectable nitroxide.

SOURCE – National Institutes of Health, Bethesda, MD

(US).

REFERENCES

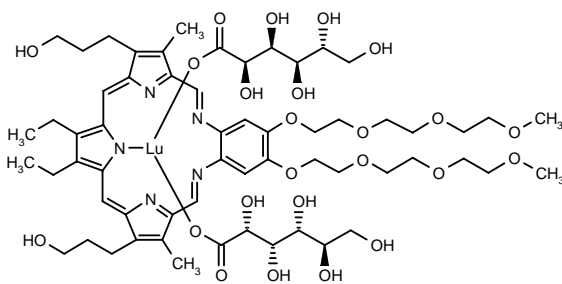
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2. Yordanov, A.T. et al. *Acyl-protected hydroxylamines as spin label generators for EPR brain imaging*. J Med Chem 2002, 45(11): 2283.

318532

[9,10-Diethyl-20,21-bis[2-[2-(2-methoxyethoxy)ethoxy]-ethoxy]-4,15-dimethyl-8,11-imino-3,6:16,13-dinitrilo-1,18-benzodiazacycloeicosine-5,14-dipropanolato-*N*¹,*N*¹⁸,*N*²³,*N*²⁴,*N*²⁵]bis(gluconato-*O*)lutetium

Lu-TeX bis(gluconate)



C60 H88 Lu N5 O24; Mol wt: 1438.3360

ACTION – Metallotexaphyrin with potential as an imaging agent, radiosensitizer, chemosensitizer and/or photosensitizer for use in the diagnosis and treatment of diseases resulting from the presence of neoplastic tissue, neovascularization or atheroma, and particularly in the fields of oncology, atherosclerosis and ophthalmology.

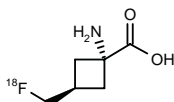
SOURCE – Pharmacyclics.

REFERENCES

1. Mody, T.D. and Galanter, J. (Pharmacyclics, Inc.) *Novel metallotexaphyrin derivs*. WO 0217908.

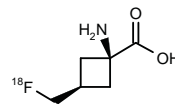
319832

trans-1-Amino-3-([¹⁸F]fluoromethyl)cyclobutane-carboxylic acid



C6 H10 F N O2; Mol wt: 146.1500

ACTION – Agent for imaging brain tumors, an [¹⁸F]-labeled amino acid that enters gliosarcoma 9L cells predominantly via L-type substrates. It showed high uptake and prolonged retention in intracranial gliosarcoma 9L tumors in rats and low uptake in normal brain tissue. Potentially useful for the detection of intracranial tumors via positron emission tomography (PET). Another related compound is:



319829: C6 H10 F N O2

SOURCE – Emory University, Atlanta, GA (US).

REFERENCES

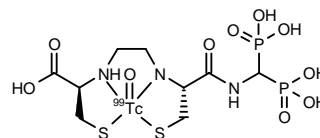
1. Goodman, M.M. and Shoup, T. (Emory University) *Amino acid analogs for tumor imaging*. WO 9717092.

2. Martarello, L. et al. *Synthesis of syn- and anti-1-amino-3-[¹⁸F]fluoromethylcyclobutane-1-carboxylic acid (FMACBC9, potential PET ligands for tumor detection*. J Med Chem 2002, 45(11): 2250.

^{99m}Tc-EC-AMDP

319982

[[*(5R,10R)*-1,1-Dihydroxy-5,10-bis(sulfanylmethyl)-1-oxido-4-oxo-2-phosphono-3,6,9-triaza-1-phosphundecan-11-oate](3-)-*N*⁶,*N*⁹,*S*,*S*']oxotechnetium-^{99m}Tc



C9 H18 N3 O10 P2 S2 Tc; Mol wt: 553.3322

ACTION – Bone tracer, a conjugate of the renal tracer [^{99m}Tc]-ethylene dicysteine covalently bound to aminomethylenediphosphonic acid (AMDP). The tracer showed efficient bone uptake and rapid clearance from blood and soft tissue by renal excretion. In rabbits and baboons scintigraphic images showed good-quality bone scans with clear visualization of skeleton and low tissue activity at 1-2 h after injection.

SOURCES – Katholieke Universiteit Leuven, Leuven (BE); Rega Institute for Medical Research, Leuven (BE).

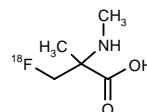
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1. Verbeke, K. et al. *Development of a conjugate of Tc-99m-EC with aminomethylenediphosphonate in the search for a bone tracer with fast clearance from soft tissue*. Bioconjugate Chem 2002, 13(1): 16.

[¹⁸F]-N-Me-FAMP²

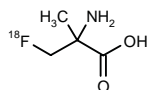
319837

3-([¹⁸F]Fluoro)-2-methyl-2-(methylamino)propionic acid



C5 H10 F N O2; Mol wt: 134.1390

ACTION – Imaging agent for the detection of intracranial neoplasms via positron emission tomography (PET). This [^{18}F]-labeled amino acid entered gliosarcoma 9L cells predominantly via the A-type amino acid transport system. Biodistribution studies showed rapid and persistent accumulation of radioactivity in rodent brain tumors with ratios of 104:1 and 97:1 in tumors versus normal brain at 60 and 120 min, respectively. Another related compound is:



[^{18}F]-FAMP [319836]^{1,2}: C₄ H₈ F N O₂

SOURCE – Emory University, Atlanta, GA (US).

REFERENCES

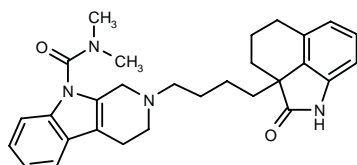
1. Goodman, M.M. and Shoup, T. (Emory University) *Amino acid analogs for tumor imaging*. WO 9717092.
2. McConathy, J. et al. *Radiolabeled amino acids for tumor imaging with PET: Radiosynthesis and biological evaluation of 2-amino-3-[^{18}F]fluoro-2-methylpropanoic acid and 3-[^{18}F]fluoro-2-methyl-2-(methylamino)propanoic acid*. J Med Chem 2002, 45(11): 2240.

PHARMACOLOGICAL TOOLS

DR-4365

320193

N,N-Dimethyl-2-[4-[2-oxo-1,2,2a,3,4,5-hexahydrobenzo[*cd*]indol-2-yl]butyl]-2,3,4,9-tetrahydro-1*H*- β -carboline-9-carboxamide



C₂₉ H₃₄ N₄ O₂; Mol wt: 470.6136

ACTION – High-affinity ligand for 5-HT₇ receptors ($\text{pK}_i = 8.45$) with more than 280-fold selectivity over 5-HT₂ and other 5-HT receptors subtype. In a functional model of 5-HT₇ receptor activation (5-HT-induced cAMP accumulation in HEK293 cells expressing 5-HT₇ receptors), compound exhibited antagonist activity and lacked agonist activity. Potentially useful as a pharmacological tool for clarifying the biological role of the 5-HT₇ receptor.

SOURCE – Meiji Seika.

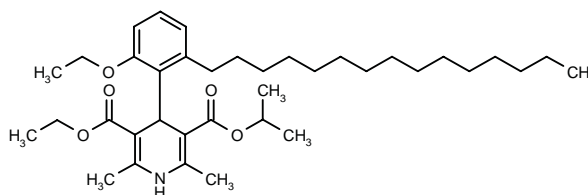
REFERENCES

1. Kikuchi, C. et al. (Meiji Seika Kaisha, Ltd.) *Tetrahydrobenzindole derivs*. EP 1057814, JP 1999189585, WO 9933804.
2. Kikuchi, C. et al. *2a-[4-(Tetrahydropyridondol-2-yl)butyl]tetrahydrobenzindole derivatives: New selective antagonists of the 5-hydroxytryptamine₇ receptor*. J Med Chem 2002, 45(11): 2197.

PPK-12

317017

4-(2-Ethoxy-6-pentadecylphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylic acid ethyl isopropyl diester



C₃₇ H₅₉ N O₅; Mol wt: 597.8751

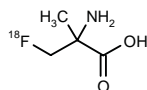
ACTION – Nifedipine analogue, a T-type and L-type calcium channel blocker ($\text{IC}_{50} = 1.65$ and $0.54 \mu\text{M}$, respectively).

SOURCES – University of Calgary, Calgary, AB (CA); Vittal Mallya Scientific Research Foundation, Bangalore (IN).

REFERENCES

1. Kumar, P.P. et al. *Synthesis and evaluation of a new class of nifedipine analogs with T-type calcium channel blocking activity*. Mol Pharmacol 2002, 61(3): 649.

ACTION – Imaging agent for the detection of intracranial neoplasms via positron emission tomography (PET). This [^{18}F]-labeled amino acid entered gliosarcoma 9L cells predominantly via the A-type amino acid transport system. Biodistribution studies showed rapid and persistent accumulation of radioactivity in rodent brain tumors with ratios of 104:1 and 97:1 in tumors versus normal brain at 60 and 120 min, respectively. Another related compound is:



[^{18}F]-FAMP [319836]^{1,2}: C₄ H₈ F N O₂

SOURCE – Emory University, Atlanta, GA (US).

REFERENCES

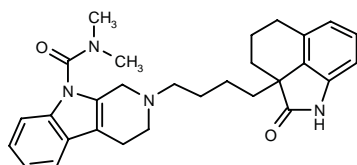
1. Goodman, M.M. and Shoup, T. (Emory University) *Amino acid analogs for tumor imaging*. WO 9717092.
2. McConathy, J. et al. *Radiolabeled amino acids for tumor imaging with PET: Radiosynthesis and biological evaluation of 2-amino-3-[^{18}F]fluoro-2-methylpropanoic acid and 3-[^{18}F]fluoro-2-methyl-2-(methylamino)propanoic acid*. J Med Chem 2002, 45(11): 2240.

PHARMACOLOGICAL TOOLS

DR-4365

320193

N,N-Dimethyl-2-[4-[2-oxo-1,2,2a,3,4,5-hexahydrobenzo[*cd*]indol-2-yl]butyl]-2,3,4,9-tetrahydro-1*H*- β -carboline-9-carboxamide



C₂₉ H₃₄ N₄ O₂; Mol wt: 470.6136

ACTION – High-affinity ligand for 5-HT₇ receptors ($\text{pK}_i = 8.45$) with more than 280-fold selectivity over 5-HT₂ and other 5-HT receptors subtype. In a functional model of 5-HT₇ receptor activation (5-HT-induced cAMP accumulation in HEK293 cells expressing 5-HT₇ receptors), compound exhibited antagonist activity and lacked agonist activity. Potentially useful as a pharmacological tool for clarifying the biological role of the 5-HT₇ receptor.

SOURCE – Meiji Seika.

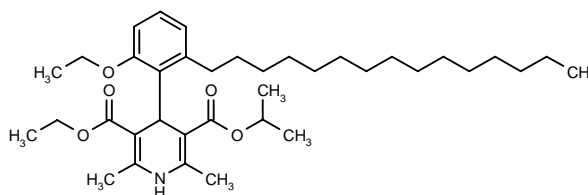
REFERENCES

1. Kikuchi, C. et al. (Meiji Seika Kaisha, Ltd.) *Tetrahydrobenzindole derivs*. EP 1057814, JP 1999189585, WO 9933804.
2. Kikuchi, C. et al. *2a-[4-(Tetrahydropyridondol-2-yl)butyl]tetrahydrobenzindole derivatives: New selective antagonists of the 5-hydroxytryptamine₇ receptor*. J Med Chem 2002, 45(11): 2197.

PPK-12

317017

4-(2-Ethoxy-6-pentadecylphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylic acid ethyl isopropyl diester



C₃₇ H₅₉ N O₅; Mol wt: 597.8751

ACTION – Nifedipine analogue, a T-type and L-type calcium channel blocker ($\text{IC}_{50} = 1.65$ and $0.54 \mu\text{M}$, respectively).

SOURCES – University of Calgary, Calgary, AB (CA); Vittal Mallya Scientific Research Foundation, Bangalore (IN).

REFERENCES

1. Kumar, P.P. et al. *Synthesis and evaluation of a new class of nifedipine analogs with T-type calcium channel blocking activity*. Mol Pharmacol 2002, 61(3): 649.

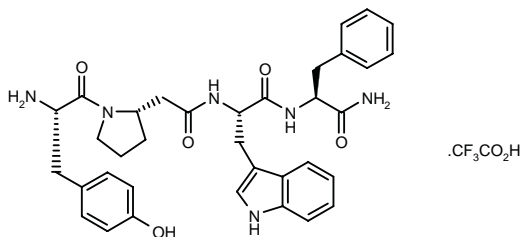
ANALGESIC AND ANESTHETIC DRUGS

ANALGESIC DRUGS

319573

N-[2-[1-(*L*-Tyrosyl)pyrrolidin-2(*S*)-yl]acetyl]-*L*-tryptophyl-*L*-phenylalaninamide trifluoroacetate

L-Tyrosyl-*L*-β-prolyl-*L*-tryptophyl-*L*-phenylalaninamide trifluoroacetate



C35 H40 N6 O5 . C2 H F3 O2; Mol wt: 738.7599

ACTION – Tetrapeptide analogue of endomorphin-1 with high affinity for ($K_i = 2.1$ nM) and functional agonist activity at ($IC_{50} = 1.10$ nM for inhibition of forskolin-induced cAMP production in SH-SY5Y cells) μ opioid receptors. Its agonist activity was comparable to that of DAMGO and was antagonized by the opioid antagonist naloxone. Compound exhibited high resistance to enzymatic degradation by α -chymotrypsin, aminopeptidase M and carboxypeptidase Y. Potentially useful as an analgesic agent.

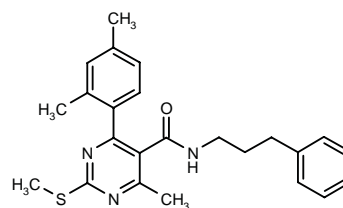
SOURCE – Università degli Studi di Bologna, Bologna (IT).

REFERENCES

- Cardillo, G. et al. *Endomorphin-1 analogues containing β-proline are μ-opioid receptor agonists and display enhanced enzymatic hydrolysis resistance.* J Med Chem 2002, 45(12): 2571.

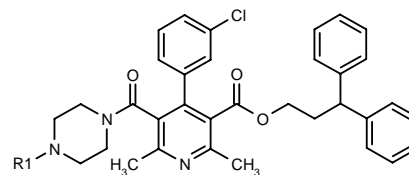
319756

4-(2,4-Dimethylphenyl)-6-methyl-2-(methylsulfanyl)-*N*-(3-phenylpropyl)pyrimidine-5-carboxamide



C24 H27 N3 O S; Mol wt: 405.5633

ACTION – Calcium channel blocker shown to inhibit N-type calcium channels in human neuroblastoma IMR-32 cells by 63% at 10 μ M and to give a pIC_{50} of 5.3 against L-type calcium channels in rat thoracic aorta preparations. In the rat formalin test, it was active at an oral dose of 3 mg/kg, indicating analgesic activity. Also potentially useful for the treatment of encephalopathies associated with ischemia or head injury, neurodegenerative disorders such as Alzheimer's disease, AIDS dementia, Parkinson's disease, cerebrovascular dementia and amyotrophic lateral sclerosis, pain, bronchial asthma, unstable angina, irritable bowel disease and drug withdrawal symptoms. Other exemplified compounds are:



Compound	R1	Formula
319759	H	C ₃₄ H ₃₄ ClN ₃ O ₃
319761	Me	C ₃₅ H ₃₆ ClN ₃ O ₃

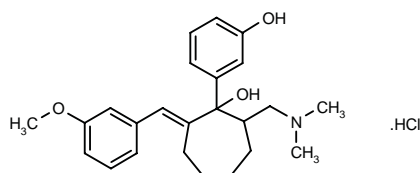
SOURCE – Ajinomoto.

REFERENCES

- Ohno, S. et al. (Ajinomoto Co., Inc.) *Novel pyrimidine deriv. and novel pyridine deriv.* WO 0222588.

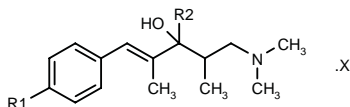
319936

2-(Dimethylaminomethyl)-1-(3-hydroxyphenyl)-7-(3-methoxybenzylidene)cycloheptanol hydrochloride

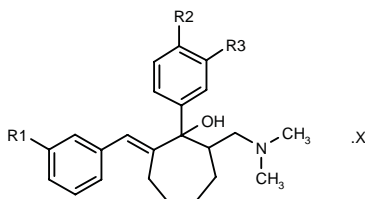


C₂₄ H₃₁ N O₃ . HCl; Mol wt: 417.9738

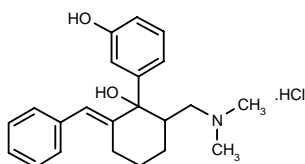
ACTION – An inhibitor of the binding of gabapentin to its receptors, demonstrating *in vivo* activity in the mouse writhing test at a dose of 10 mg/kg i.v. Potentially useful for the treatment of acute, chronic and neuropathic pain, as well as other disorders such as epilepsy, hot flashes, postmenopausal syndrome, amyotrophic lateral sclerosis, reflex sympathetic dystrophy, anxiety, bipolar disorder, depression, diabetic neuropathy, multiple sclerosis, Parkinson's disease, Alzheimer's disease, Huntington's disease, etc. Other exemplified 5-amino-1-penten-3-ol derivatives include the following:



Compound	R1	R2	X	Formula
319939	H	Ph		C ₂₁ H ₂₇ NO
319940	H	3-Me-PhCH ₂		C ₂₃ H ₃₁ NO
319941	H	3-Cl-PhCH ₂		C ₂₂ H ₂₆ ClNO
319942	F	3-MeO-PhCH ₂		C ₂₃ H ₃₀ FNO ₂
319943	Cl	3-MeO-PhCH ₂		C ₂₃ H ₃₀ ClNO ₂
319948	H	3-OH-Ph	HCl	C ₂₁ H ₂₇ NO ₂ ·HCl
319949	H	4-Cl-PhCH ₂	HCl	C ₂₂ H ₂₆ ClNO·HCl
319950	H	3-MeO-Ph	HCl	C ₂₂ H ₂₉ NO ₂ ·HCl



Compound	R1	R2	R3	X	Formula
319944	OMe	OMe	H		C ₂₅ H ₃₃ NO ₃
319945	OMe	Cl	H		C ₂₄ H ₃₀ ClNO ₂
319946	H	H	OH	HCl	C ₂₃ H ₂₉ NO ₂ ·HCl
319947	H	H	OMe	HCl	C ₂₄ H ₃₁ NO ₂ ·HCl



319951: C₂₂ H₂₇ N O₂ . H Cl

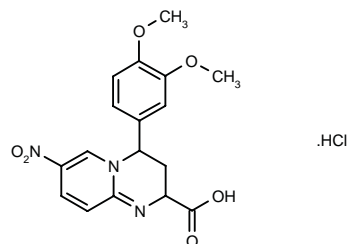
SOURCE – Grünenthal.

REFERENCES

1. Buschmann, H. et al. (Grünenthal GmbH) *Substd. 5-amino-1-penten-3-ol derivs.* DE 10048714, WO 0228816, WO 0230869.

320326

4-(3,4-Dimethoxyphenyl)-7-nitro-3,4-dihydro-2H-pyrido-[1,2-a]pyrimidine-2-carboxylic acid hydrochloride



C₁₇ H₁₇ N₃ O₆ . HCl; Mol wt: 395.7972

ACTION – Analgesic agent, a representative compound from a series of pyrido[1,2-a]pyrimidine derivatives. Potentially useful for the treatment of pain, as well as urinary incontinence, pruritus, tinnitus aurium and diarrhea.

SOURCE – Grünenthal.

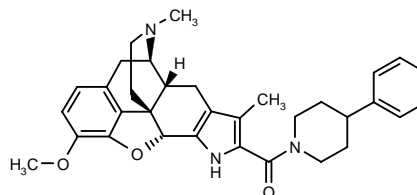
REFERENCES

1. Gerlach, M. et al. (Grünenthal GmbH) *Substd. 3,4-dihydro-pyrido[1,2-a]pyrimidines.* DE 10050662, WO 0230933.

320386

1-[(4b*S*,8*R*,8a*R*,12b*R*)-1-Methoxy-7,10-dimethyl-5,6,7,8a,9,12,12b-octahydro-4,8-methano[1]benzofuro-[3,2-*e*]pyrrolo[2,3-*g*]isoquinolin-11-yl]-1-(4-phenylpiperidin-1-yl)methanone

4,5-Epoxy-3-methoxy-4',17-dimethyl-5'-(4-phenylpiperidin-1-ylcarbonyl)pyrrolo[2',3':6,7]morphinan



C₃₃ H₃₇ N₃ O₃; Mol wt: 523.6733

ACTION – A representative compound from a series of morphinoid derivatives with affinity for delta opioid receptors. Potentially useful as an analgesic agent, and also in the treatment of transplant rejection, allergy, inflammation, drug and alcohol abuse, neurodegenerative disorders, cardiovascular and respiratory diseases, cough, mental illness, epilepsy and gastrointestinal disorders such as gastritis, diarrhea and irritable bowel syndrome.

SOURCE – GlaxoSmithKline.

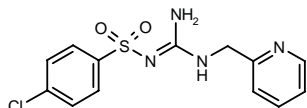
REFERENCES

1. Dondio, G. et al. (GlaxoSmithKline SpA) *Pyrrole-condensed morphinoid derivs.* WO 0230936.

320519

N-[1-Amino-1-(pyridin-2-ylmethylamino)methylene]-4-chlorobenzenesulfonamide

2-(4-Chlorophenylsulfonyl)-1-(pyridin-2-ylmethyl)-guanidine



C13 H13 Cl N4 O2 S; Mol wt: 324.7907

ACTION – Agent with affinity for gabapentin receptors ($IC_{50} = 779$ nM) and analgesic activity. When tested *in vivo* for activity in the formalin test, compound gave ED_{50} values of 13.3 mg/kg and 97 mg/kg, respectively, in rats and mice. Potentially useful for the treatment of neuropathic, acute and chronic pain, epilepsy, migraine, hyperalgesia and allodynia, as well as other disorders including postmenopausal syndrome, amyotrophic lateral sclerosis, bipolar disorder, anxiety, depression, diabetic neuropathy, multiple sclerosis, Parkinson's disease, Alzheimer's disease, gastrointestinal disorders, etc.

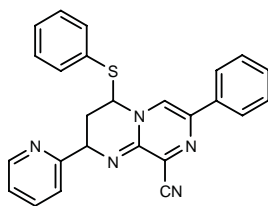
SOURCE – Grünenthal.

REFERENCES

1. Gerlach, M. et al. (Grünenthal GmbH) *Sulfonylguanidine.* WO 0230881.

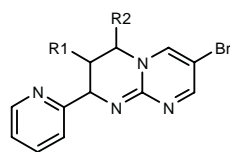
320576

7-Phenyl-4-(phenylsulfanyl)-2-(2-pyridyl)-3,4-dihydro-2H-pyrazino[1,2-a]pyrimidine-9-carbonitrile

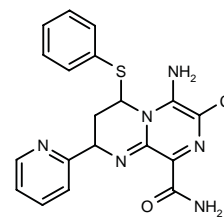


C25 H19 N5 S; Mol wt: 421.5261

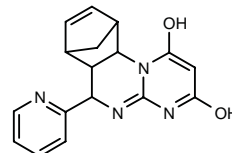
ACTION – Agent with affinity for mu opioid receptors ($K_i = 1.4$ μ M), potentially useful for the treatment of pain, urinary incontinence, pruritus, tinnitus aurium and diarrhea. Other exemplified compounds are:



Compound	R1	R2	Formula
320578	H	SPh	C ₁₈ H ₁₅ BrN ₄ S
320581	-CH ₂ CH ₂ CH=CH-		C ₁₆ H ₁₅ BrN ₄



320577: C19 H17 Cl N6 O S



320579: C17 H16 N4 O2

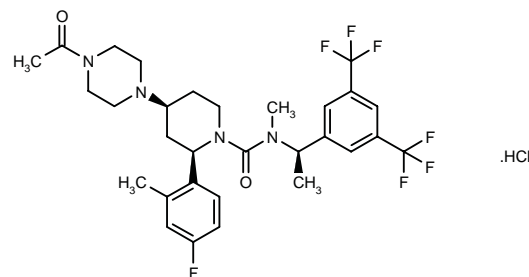
SOURCE – Grünenthal.

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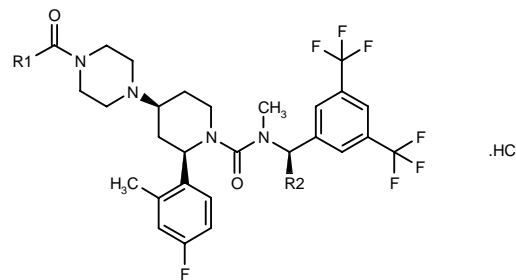
320922

4-(S)-(4-Acetylpiperazin-1-yl)-N-[1(R)-[3,5-bis-(trifluoromethyl)phenyl]ethyl]-2(R)-(4-fluoro-2-methylphenyl)-N-methylpiperidine-1-carboxamide hydrochloride



C30 H35 F7 N4 O2 . HCl; Mol wt: 653.0794

ACTION – Tachykinin antagonist that displayed a pK_i of 10.29 against NK_1 receptors expressed in CHO cells, and demonstrated *in vivo* NK_1 -antagonist activity in the gerbil foot-tapping model, with an oral ED_{50} of 0.05 mg/kg. Potentially useful for the treatment of a broad range of tachykinin-mediated disorders including depression, anxiety, panic, Alzheimer's disease, drug abuse, pain, sleep disorders, inflammatory disorders such as asthma and rheumatoid arthritis, allergic disorders such as urticaria and rhinitis, and emesis. Other exemplified compounds are:



Compound	R1	R2	Formula
320923	Me	H	C ₂₉ H ₃₃ F ₇ N ₄ O ₂ .HCl
320924	cyclopropyl	Me	C ₃₂ H ₃₇ F ₇ N ₄ O ₂ .HCl

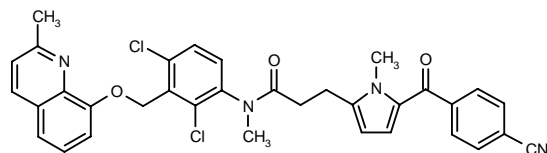
SOURCE – GlaxoSmithKline.

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320991

3-[5-(4-Cyanobenzoyl)-1-methyl-1H-pyrrol-2-yl]-N-(2,4-dichloro-3-(2-methylquinolin-8-yloxymethyl)phenyl)-N-methylpropionamide



C34 H28 Cl2 N4 O3; Mol wt: 611.5262

ACTION – Bradykinin B₂ receptor antagonist with nanomolar affinity for the receptor and efficacy in animal models of nociception.

SOURCE – Johnson & Johnson.

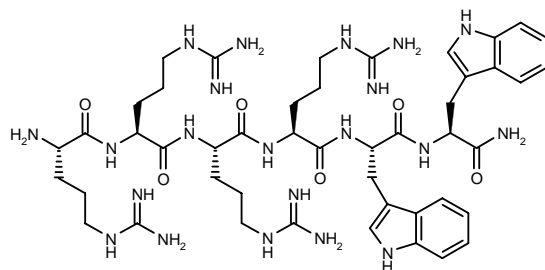
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321413

L-Arginyl-L-arginyl-L-arginyl-L-arginyl-L-tryptophyl-L-tryptophamide

L-R4W2



C46 H71 N21 O6; Mol wt: 1014.2080

ACTION – Potent stereoselective vanilloid (capsaicin) VR1 receptor antagonist, an arginine-rich hexapeptide proven to competitively antagonize the effects of capsaicin and resiniferatoxin in primary cultures of adult rat dorsal root ganglion neurons, the L-stereoisomer being more potent than the D-stereoisomer. Potentially useful as a lead for the development of low-molecular-weight compounds with analgesic activity for the treatment of chronic pain.

SOURCE – Grünenthal.

REFERENCES

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MORPHINE SULFATE

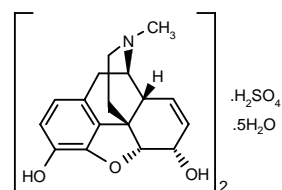
BANM, JAN, USAN

New Formulation

091342

(5α,6α)-4,5-Epoxy-17-methyl-7,8-didehydromorphinan-3,6-diol sulfate (2:1) pentahydrate

Morphelan™ (former brand name)



2 C17 H19 N O3 . 5 H2O . H2 O4 S; Mol wt: 758.8340

ACTION – Once-daily dual-release formulation of the opioid agonist morphine utilizing the Spheroidal Oral Drug Absorption System (SODAS®) technology.

INDICATION – Once-daily treatment of chronic, moderate to severe pain in patients who require continuous therapy for an extended period.

PRESENTATION – Extended-release capsules combining an immediate-release component and an extended-release component, 30, 60, 90 and 120 mg.

PROPRIETARY NAME –Avinza (US).

SOURCES – Elan; marketed by Ligand.

REFERENCES

1. Caldwell, J.R. et al. *Efficacy and safety of a once-daily morphine formulation in chronic, moderate-to-severe osteoarthritis pain: Results from a randomized, placebo-controlled, double-blind trial and an open-label extension trial.* J Pain Symptom Manage 2002, 23(4): 278.
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ANTIMIGRAINE DRUGS

FROVATRIPTAN

Prop INN, USAN

212285

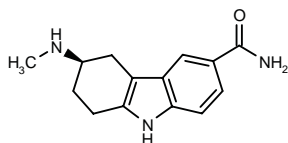
(R)-(+)-3-(Methylamino)-1,2,3,4-tetrahydro-9H-carbazole-6-carboxamide

SB-209509⁺

SB-209509AX (succinate)

VML-251

Migard®



C14 H17 N3 O; Mol wt: 243.3110

ACTION – Potent and selective 5-HT_{1B/1D} receptor agonist.

INDICATION – Acute treatment of migraine with or without aura.

PRESENTATION – Tablets, 3.91 mg frovatriptan succinate equivalent to 2.5 mg base.

PROPRIETARY NAME – Frova (US).

SOURCES – Vernalis; marketed by Elan and UCB Pharma.

RECENT REFERENCES

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2. Carel, I. et al. *Comparative effects of frovatriptan and sumatriptan on coronary and internal carotid vascular haemodynamics in conscious dogs.* Br J Pharmacol 2001, 132(5): 1071.

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4. Geraud, G. and Keywood, C. *Tolerability of frovatriptan during short and long-term use for acute migraine and in comparison with sumatriptan.* Cephalalgia 2000, 20(4): Abst 225.

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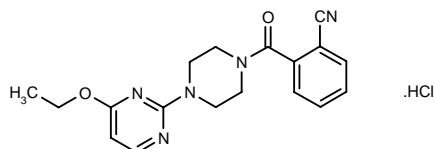
MONOGRAPH – Graul, A. et al. *SB-209509/VML-251.* Drugs Fut 1997, 22(7): 0725.

⁺Drug Data Rep 1997, 019(02): 0112.

ANESTHETIC DRUGS

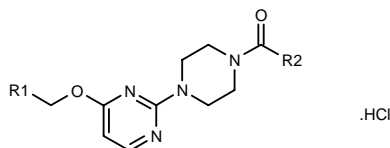
320584

2-[4-(4-Ethoxypyrimidin-2-yl)piperazin-1-ylcarbonyl]-benzonitrile hydrochloride



C₁₈ H₁₉ N₅ O₂ . HCl; Mol wt: 373.8420

ACTION – Sedative/hypnotic agent with anesthetic properties, as demonstrated in several animal studies. It was also shown to act as an anticonvulsant (ED₅₀ = 25.1 mg/kg i.p.), sedative and muscle relaxant in mice following i.p. administration. Other exemplified compounds are:



Compound	R1	R2	Formula
320585	H	2-CN-Ph	C ₁₇ H ₁₇ N ₅ O ₂ .HCl
320586	Et	2-CN-Ph	C ₁₉ H ₂₁ N ₅ O ₂ .HCl
320587	Pr	2-CN-Ph	C ₂₀ H ₂₃ N ₅ O ₂ .HCl
320588	Me	3-CN-2-thienyl	C ₁₆ H ₁₇ N ₅ O ₂ S.HCl
320589	Et	3-CN-2-thienyl	C ₁₇ H ₁₉ N ₅ O ₂ S.HCl
320590	Me	3-CN-2-Pyr	C ₁₇ H ₁₈ N ₅ O ₂ .HCl
320591	Et	3-CN-2-Pyr	C ₁₈ H ₂₀ N ₅ O ₂ .HCl

SOURCE – Esteve.

REFERENCES

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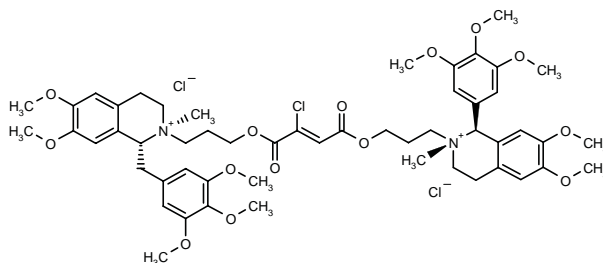
ADJUNCTS TO ANESTHESIA

GW-280430A*

269760

(Z)-2-Chlorofumaric acid 1-[3-[6,7-dimethoxy-2(S)-methyl-1(R)-(3,4,5-trimethoxybenzyl)-1,2,3,4-tetrahydroisoquinolinium-2-yl]propyl] 4-[3-[6,7-dimethoxy-2(R)-methyl-1(S)-(3,4,5-trimethoxyphenyl)-1,2,3,4-tetrahydroisoquinolinium-2-yl]propyl] diester dichloride

GW-0430



C₅₃ H₆₉ Cl₃ N₂ O₁₄; Mol wt: 1064.4870

ACTION – Ultra-short-acting nondepolarizing neuromuscular blocker able to induce neuromuscular block in monkeys (ED₉₅ = 63 µg/kg i.v.) with a rapid onset (88 s) and short duration of action (5.6 min), without affecting blood pressure and heart rate. Preliminary clinical data in healthy volunteers comparing the neuromuscular blocking properties of compound and rocuronium showed a more rapid onset and duration of action for compound than for the reference drug, with a pattern of blockade similar to that of succinylcholine. Potentially useful as an adjunct to general anesthesia or to provide general muscle relaxation during surgical procedures.

SOURCES – Avera Pharmaceuticals; Cornell Research Foundation, Ithaca, NY (US); GlaxoSmithKline.

REFERENCES

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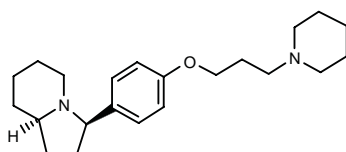
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PSYCHOPHARMACOLOGIC DRUGS

TREATMENT OF SLEEP DISORDERS

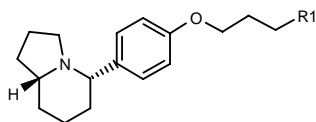
320170

(3*R*,8*aR*)-3-[4-[3-(1-Piperidiny)propoxy]phenyl]perhydro-indolizine

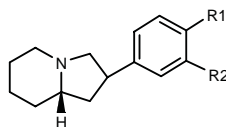


C₂₂H₃₄N₂O; Mol wt: 342.5236

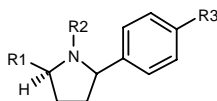
ACTION – Modulator of histamine H₃ receptors (K_i = 0.06 nM), potentially useful for the treatment of sleep/awake disorders, narcolepsy, arousal/vigilance disorders, attention deficit hyperactivity disorder, dementia, mild cognitive impairment, cognitive dysfunction, schizophrenia, depression, manic disorder, bipolar disorders, upper airways allergic responses, nasal congestion and allergic rhinitis. Other exemplified compounds are:



Compound	R1	Formula
320171	1-Pip-CH ₂	C ₂₃ H ₃₆ N ₂ O
320172	1-Pip	C ₂₂ H ₃₄ N ₂ O



Compound	R1	R2	Isomer	Formula
320173	1-Pip-(CH ₂) ₃ O	H	trans	C ₂₂ H ₃₄ N ₂ O
320174	1-Pip-(CH ₂) ₃ O	H	cis	C ₂₂ H ₃₄ N ₂ O
320175	H	1-Pip-(CH ₂) ₃ O	trans	C ₂₂ H ₃₄ N ₂ O



Compound	R1	R2	R3	Isomer	Formula
320176	-(CH ₂) ₄ -	1-Pip-(CH ₂) ₃ O		cis	C ₂₂ H ₃₄ N ₂ O
320177	-(CH ₂) ₄ -	1-Pip-(CH ₂) ₃ O		3 <i>S</i> ,8 <i>aS</i>	C ₂₂ H ₃₄ N ₂ O
320178	-(CH ₂) ₄ -	1-Pip-(CH ₂) ₅ NH		cis	C ₂₄ H ₃₈ N ₃
320179	-(CH ₂) ₃ -	1-Pip-(CH ₂) ₃ O			C ₂₁ H ₃₂ N ₂ O

SOURCE – Ortho-McNeil.

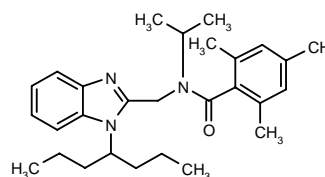
REFERENCES

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ANXIOLYTICS

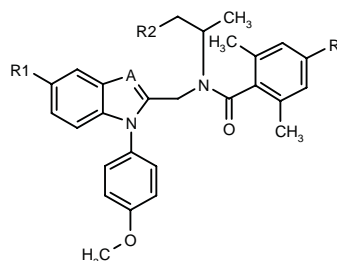
319874

N-Isopropyl-2,4,6-trimethyl-*N*-[1-(1-propylbutyl)-1*H*-benzimidazol-2-ylmethyl]benzamide

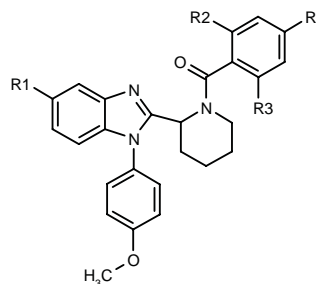


C₂₈H₃₉N₃O; Mol wt: 433.6361

ACTION – Agent with affinity for corticotropin-releasing factor (CRF) receptors, particularly CRF₁, reported to be useful for the treatment of anxiety, stress-related disorders, eating disorders, depression and bipolar disorder. Other exemplified compounds within this series of indole- or benzimidazole-containing aromatic carbox-amides are:



Compound	R1	R2	R3	A	Formula
319875	CF ₃	OH	Me	N	C ₂₉ H ₃₀ F ₃ N ₃ O ₃
319879	H	H	Me	CH	C ₂₉ H ₃₂ N ₂ O ₂
319880	H	H	OMe	N	C ₂₈ H ₃₁ N ₃ O ₃
319886	F	H	Me	N	C ₂₈ H ₃₀ FN ₃ O ₂



Compound	R1	R2	R3	R4	Formula
319876	H	H	OMe	OMe	C ₂₈ H ₂₉ N ₃ O ₄
319881	F	Me	Me	Me	C ₂₉ H ₃₀ FN ₃ O ₂
319884	CH ₂ N(Et) ₂	Me	Me	Me	C ₃₄ H ₄₂ N ₄ O ₂
319885	NH ₂	Me	Me	Me	C ₂₉ H ₃₂ N ₄ O ₂

8. Glaxo Wellcome's R&D pipeline remains full and diverse. DailyDrugNews.com (Daily Essentials) 1998, Jan 21.

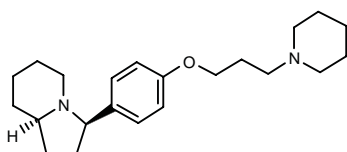
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PSYCHOPHARMACOLOGIC DRUGS

TREATMENT OF SLEEP DISORDERS

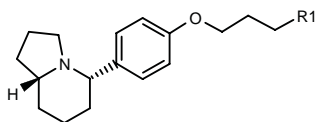
320170

(3*R*,8*aR*)-3-[4-[3-(1-Piperidinyl)propoxy]phenyl]perhydro-indolizine

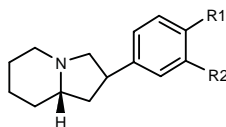


C₂₂H₃₄N₂O; Mol wt: 342.5236

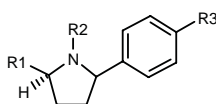
ACTION – Modulator of histamine H₃ receptors (K_i = 0.06 nM), potentially useful for the treatment of sleep/awake disorders, narcolepsy, arousal/vigilance disorders, attention deficit hyperactivity disorder, dementia, mild cognitive impairment, cognitive dysfunction, schizophrenia, depression, manic disorder, bipolar disorders, upper airways allergic responses, nasal congestion and allergic rhinitis. Other exemplified compounds are:



Compound	R1	Formula
320171	1-Pip-CH ₂	C ₂₃ H ₃₆ N ₂ O
320172	1-Pip	C ₂₂ H ₃₄ N ₂ O



Compound	R1	R2	Isomer	Formula
320173	1-Pip-(CH ₂) ₃ O	H	trans	C ₂₂ H ₃₄ N ₂ O
320174	1-Pip-(CH ₂) ₃ O	H	cis	C ₂₂ H ₃₄ N ₂ O
320175	H	1-Pip-(CH ₂) ₃ O	trans	C ₂₂ H ₃₄ N ₂ O



Compound	R1	R2	R3	Isomer	Formula
320176	-(CH ₂) ₄ -	1-Pip-(CH ₂) ₃ O	cis		C ₂₂ H ₃₄ N ₂ O
320177	-(CH ₂) ₄ -	1-Pip-(CH ₂) ₃ O	3 <i>S</i> ,8 <i>aS</i>		C ₂₂ H ₃₄ N ₂ O
320178	-(CH ₂) ₄ -	1-Pip-(CH ₂) ₅ NH	cis		C ₂₄ H ₃₈ N ₃
320179	-(CH ₂) ₃ -	1-Pip-(CH ₂) ₃ O			C ₂₁ H ₃₂ N ₂ O

SOURCE – Ortho-McNeil.

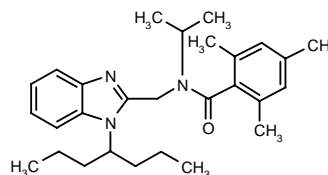
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ANXIOLYTICS

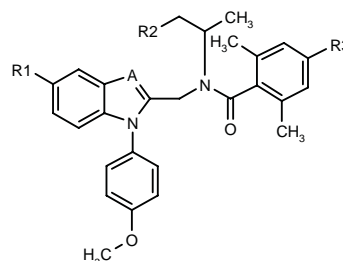
319874

N-Isopropyl-2,4,6-trimethyl-*N*-[1-(1-propylbutyl)-1*H*-benzimidazol-2-ylmethyl]benzamide

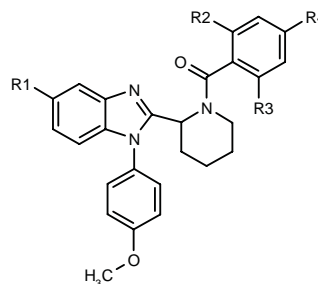


C₂₈H₃₉N₃O; Mol wt: 433.6361

ACTION – Agent with affinity for corticotropin-releasing factor (CRF) receptors, particularly CRF₁, reported to be useful for the treatment of anxiety, stress-related disorders, eating disorders, depression and bipolar disorder. Other exemplified compounds within this series of indole- or benzimidazole-containing aromatic carbox-amides are:



Compound	R1	R2	R3	A	Formula
319875	CF ₃	OH	Me	N	C ₂₉ H ₃₀ F ₃ N ₃ O ₃
319879	H	H	Me	CH	C ₂₉ H ₃₂ N ₂ O ₂
319880	H	H	OMe	N	C ₂₈ H ₃₁ N ₃ O ₃
319886	F	H	Me	N	C ₂₈ H ₃₀ FN ₃ O ₂



Compound	R1	R2	R3	R4	Formula
319876	H	H	OMe	OMe	C ₂₈ H ₂₉ N ₃ O ₄
319881	F	Me	Me	Me	C ₂₉ H ₃₀ FN ₃ O ₂
319884	CH ₂ N(Et) ₂	Me	Me	Me	C ₃₄ H ₄₂ N ₄ O ₂
319885	NH ₂	Me	Me	Me	C ₂₉ H ₃₂ N ₄ O ₂

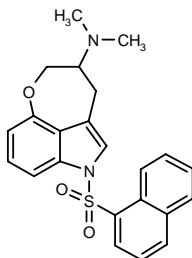
SOURCE – Neurogen.

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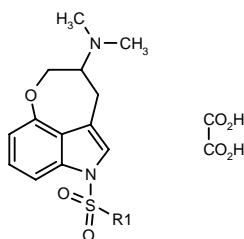
320028

N,N-Dimethyl-6-(naphthalen-1-ylsulfonyl)-2,3,4,6-tetrahydrooxepino[4,3,2-*cd*]indol-3-amine



C23 H22 N2 O3 S; Mol wt: 406.5038

ACTION – Agent with selective affinity for the 5-HT₆ receptor subtype that gave a K_i of 0.49 nM against 5-HT₆ receptors in rat brain preparations. Potentially useful for the treatment of sleep disorders, anxiety, neurosis, schizophrenia, stroke, dementia, pain, Alzheimer's disease, Parkinson's disease, depression, anxiety and migraine, among other CNS disorders. Other exemplified tricyclic compounds are:



Compound	R1	Formula
320029	Ph	C ₁₉ H ₂₀ N ₂ O ₃ S.C ₂ H ₂ O ₄
320030	5-Cl-2-thienyl	C ₁₇ H ₁₇ ClN ₂ O ₃ S ₂ .C ₂ H ₂ O ₄

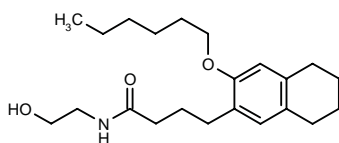
SOURCE – Shionogi.

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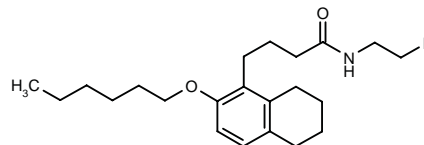
320110

4-[3-(Hexyloxy)-5,6,7,8-tetrahydronaphthalen-2-yl]-*N*-(2-hydroxyethyl)butyramide

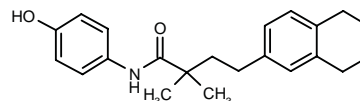


C22 H35 N O3; Mol wt: 361.5225

ACTION – Modulator of endocannabinoid receptors activated by anandamide, particularly cannabinoid CB₁ and CB₂ receptors, and the anandamide transporter. Potentially useful for the treatment of anxiety, pain, glaucoma, depression, eating disorders, psychosis and muscle spasms. Other exemplified compound are:



320111: C22 H34 F N O2



320112: C22 H27 N O2

SOURCE – Lilly.

REFERENCES

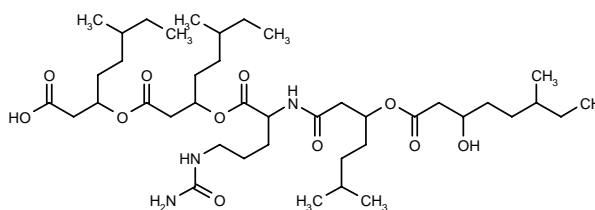
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ANTIPSYCHOTIC DRUGS

CITRULLIMYCINE A

319677

3-[3-[*N*⁵-Carbamoyl-*N*²-[3-(3-hydroxy-6-methyloctanoyloxy)-6-methylheptanoyl]-DL-ornithyloxy]-6-methyloctanoyloxy]-6-methyloctanoic acid



C41 H75 N3 O11; Mol wt: 786.0535

ACTION – Agent with affinity for neurotensin receptors isolated from cultures of *Streptomyces* sp. ST 10396 (DSM 13309). It inhibited the binding of [³H]-neurotensin to its receptors with an IC₅₀ of 16 μM. Potentially useful for the treatment of schizophrenia, Parkinson's disease and Alzheimer's disease.

SOURCE – Aventis Pharma.

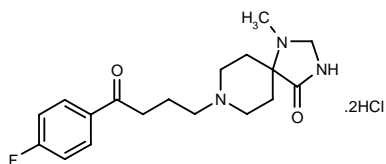
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KML-010

270826

8-[4-(4-Fluorophenyl)-4-oxobutyl]-1-methyl-1,3,8-triazaspiro[4.5]decan-4-one dihydrochloride



C₁₈ H₂₄ F N₃ O₂ . 2HCl; Mol wt: 406.3264

ACTION – High-affinity ligand for 5-HT_{2A} receptors (K_i = 23 nM) with high selectivity over 5-HT_{2C} and 5-HT_{1A} receptors (K_i > 10,000 nM) and good selectivity versus dopamine D₂ receptors (K_i = 220 nM). Potentially useful as an antipsychotic and antidepressant.

SOURCES – Albany Medical College, Albany, NY (US); Virginia Commonwealth University, Richmond, VA (US).

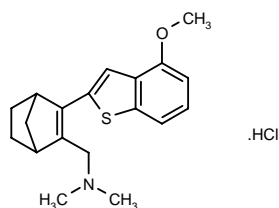
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TREATMENT OF MOOD DISORDERS

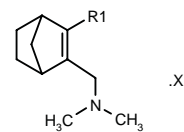
319747

(±)-*N*-[3-(4-Methoxy-1-benzothien-2-yl)bicyclo[2.2.1]hept-2-en-2-ylmethyl]-*N,N*-dimethylamine hydrochloride

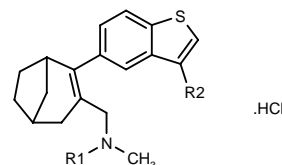


C₁₉ H₂₃ N O S . HCl; Mol wt: 349.9236

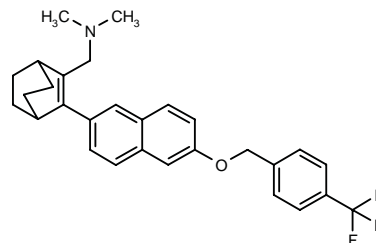
ACTION – Agent that inhibits the reuptake of 5-HT, dopamine and/or noradrenaline, with potential in the treatment of depression, obesity, bulimia, alcoholism, pain, hypertension, aging, senile dementia, Alzheimer's disease, attention deficit hyperactivity disorder, sexual dysfunction, Parkinson's disease, anxiety, chronic fatigue syndrome, panic disorders, obsessive-compulsive disorder, schizophrenia, gastrointestinal disorders, headache, cardiovascular disorders, smoking cessation, drug abuse, emesis and sleep disorders. Other exemplified compounds are:



Compound	R1	X	Formula
319748	OSO ₂ CF ₃		C ₁₁ H ₁₆ F ₃ NO ₃ S
319749	5-F-2-benzothiienyl	HCl	C ₁₈ H ₂₀ FNS.HCl
319750	7-MeO-2-benzothiienyl	HCl	C ₁₉ H ₂₃ NOS.HCl
319751	4-benzothiienyl		C ₁₈ H ₂₁ NS
319752	2-Me-5-benzothiienyl	HCl	C ₁₉ H ₂₃ NS.HCl



Compound	R1	R2	Formula
319753	Me	H	C ₁₉ H ₂₃ NS.HCl
319754	H	Me	C ₁₉ H ₂₃ NS.HCl



319755: C₂₉ H₃₀ F₃ N O

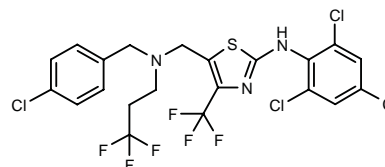
SOURCE – Lilly.

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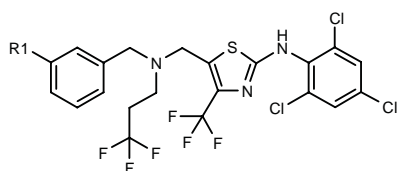
320071

5-[*N*-(4-Chlorobenzyl)-*N*-(3,3,3-trifluoropropyl)amino-methyl]-*N*-(2,4,6-trichlorophenyl)-4-(trifluoromethyl)-thiazol-2-amine



C₂₁ H₁₅ Cl₄ F₆ N₃ S; Mol wt: 597.2365

ACTION – Corticotropin-releasing factor CRF₁ receptor antagonist (IC_{50} = 4.5 nM), potentially useful for the treatment of depression, anxiety, affective disorders, eating disorders, posttraumatic stress disorder, headache, inflammation, drug abuse and drug and alcohol withdrawal symptoms. Other exemplified substituted azole derivatives are:



Compound	R1	Formula
320072	H	C ₂₁ H ₁₆ Cl ₃ F ₆ N ₃ S
320073	F	C ₂₁ H ₁₅ Cl ₃ F ₇ N ₃ S

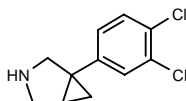
SOURCE – Bristol-Myers Squibb.

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320202

(+)-1-(3,4-Dichlorophenyl)-3-azabicyclo[3.1.0]hexane



C₁₁ H₁₁ Cl₂ N; Mol wt: 228.1209

ACTION – Antidepressant with affinity for both the noradrenaline and 5-HT transporters, giving K_i values of 142 and 118 nM, respectively.

SOURCE – DOV Pharmaceutical.

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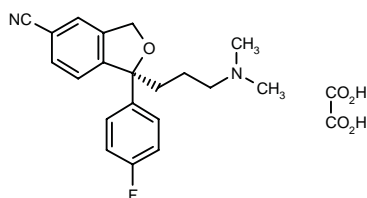
ESCITALOPRAM OXALATE

Prop INNM, USAN

157449

(+)-1-(S)-[3-(Dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile oxalate

(+)-(S)-Citalopram⁺ oxalate
Lu-26-054-0
LexaproTM



C₂₀ H₂₁ F N₂ O . C₂ H₂ O₄; Mol wt: 414.4307

ACTION – Selective serotonin reuptake inhibitor.

INDICATION – Treatment of depression and panic disorder.

PRESENTATION – Tablets, 5, 10, 15 and 20 mg.

PROPRIETARY NAME – Ciprálex (CH, GB, SE).

SOURCES – Lundbeck.

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28. *Forest reports successful completion of phase III escitalopram clinical trial.* DailyDrugNews.com (Daily Essentials) 2000, Dec 18.

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30. *Important advances in the Lundbeck pipeline during 2000.* DailyDrugNews.com (Daily Essentials) 2001, Jan 10.

31. *Lundbeck establishes various collaborative agreements just after close of first half.* DailyDrugNews.com (Daily Essentials) 1999, Aug 26.

32. *Lundbeck highlights significant events during 1999.* DailyDrugNews.com (Daily Essentials) 2000, March 16.

33. *Lundbeck licenses Ciprallex to Mochida in Japan.* DailyDrugNews.com (Daily Essentials) 2002, June 6.

34. *Lundbeck offers interim progress report.* DailyDrugNews.com (Daily Essentials) 2001, Nov 14.

35. *Lundbeck seeks first approval of Ciprallex in Sweden.* DailyDrugNews.com (Daily Essentials) 2001, Feb 8.

36. *Lundbeck's psychopharmacological drug pipeline.* DailyDrugNews.com (Daily Essentials) 2001, Sept 20.

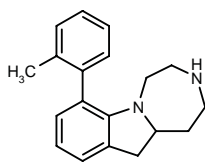
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*Drug Data Rep 1990, 012(04): 0275.

PHA-670080

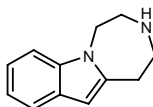
320997

7-(2-Methylphenyl)-2,3,4,5,11,11a-hexahydro-1H-[1,4]diazepino[1,7-a]indole



C19 H22 N2; Mol wt: 278.3968

ACTION – High-affinity ligand for 5-HT_{2C} receptors, potentially useful for the treatment of anxiety, depression, schizophrenia, obsessive-compulsive disorder and eating disorders. Another related azepinoindole is:



PNU-181731A [311338]: C12 H14 N2

SOURCE – Pharmacia.

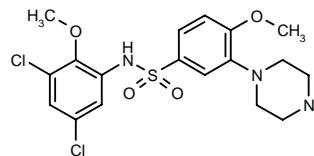
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SB-399885

321011

N-(3,5-Dichloro-2-methoxyphenyl)-4-methoxy-3-(1-piperazinyl)benzenesulfonamide



C18 H21 Cl2 N3 O4 S; Mol wt: 446.3529

ACTION – Potent and selective 5-HT₆ receptor antagonist with potential in the treatment of CNS disorders including depression, anxiety, psychosis and cognitive deficits.

SOURCE – GlaxoSmithKline.

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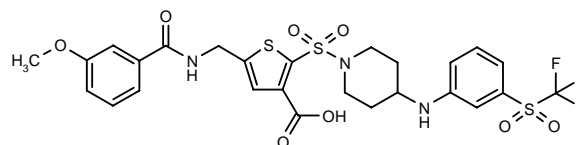
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NEUROLOGIC DRUGS

ANTIEPILEPTIC DRUGS

319778

5-(3-Methoxybenzamidoethyl)-2-[4-[3-(trifluoromethylsulfonyl)phenylamino]piperidin-1-ylsulfonyl]thiophene-3-carboxylic acid



C26 H26 F3 N3 O8 S3; Mol wt: 661.6964

ACTION – Water-soluble (0.18 mg/ml at room temperature and pH 7.4) agent that inhibits Jun kinases (JNK), particularly JNK3 (IC₅₀ < 0.1 μM). Potentially useful for the treatment of neuronal disorders such as epilepsy, Alzheimer's disease, Huntington's disease and Parkinson's disease, head and spinal cord injury, multiple sclerosis and ischemia, autoimmune disorders selected from inflammatory bowel disease, rheumatoid arthritis, asthma, septic shock and transplant rejection, retinal diseases, cancer, and also cardiovascular disorders including stroke, arteriosclerosis, myocardial infarction, myocardial reperfusion injury, renal failure and ischemic conditions. Other exemplified compounds are:

25. *Ciprallex now available for prescription in three European markets.* DailyDrugNews.com (Daily Essentials) 2002, June 14.

26. *Ciprallex/Lexapro heads for major launches by mid-2002.* DailyDrugNews.com (Daily Essentials) 2002, March 8.

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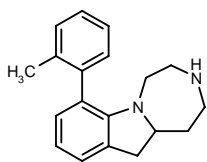
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*Drug Data Rep 1990, 012(04): 0275.

PHA-670080

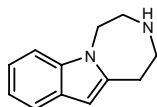
320997

7-(2-Methylphenyl)-2,3,4,5,11,11a-hexahydro-1H-[1,4]diazepino[1,7-a]indole



C19 H22 N2; Mol wt: 278.3968

ACTION – High-affinity ligand for 5-HT_{2C} receptors, potentially useful for the treatment of anxiety, depression, schizophrenia, obsessive-compulsive disorder and eating disorders. Another related azepinoindole is:



PNU-181731A [311338]: C12 H14 N2

SOURCE – Pharmacia.

REFERENCES

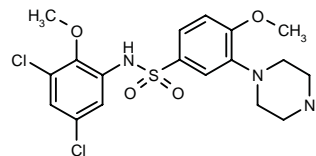
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2. Hoffman, R.L. et al. *The discovery and synthesis of a novel class of azepinoindoles with potent 5-HT_{2C} affinity: Identification, biological evaluation, and SAR of PNU-181731A.* 28th Natl Med Chem Symp (June 8-12, San Diego) 2002, Abst 14.

SB-399885

321011

N-(3,5-Dichloro-2-methoxyphenyl)-4-methoxy-3-(1-piperazinyl)benzenesulfonamide



C18 H21 Cl2 N3 O4 S; Mol wt: 446.3529

ACTION – Potent and selective 5-HT₆ receptor antagonist with potential in the treatment of CNS disorders including depression, anxiety, psychosis and cognitive deficits.

SOURCE – GlaxoSmithKline.

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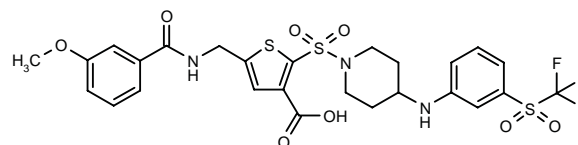
2. King, F.D. and Bromidge, S.M. *The identification of potent and selective 5-HT₆ receptor antagonists.* 28th Natl Med Chem Symp (June 8-12, San Diego) 2002, Abst.

NEUROLOGIC DRUGS

ANTIEPILEPTIC DRUGS

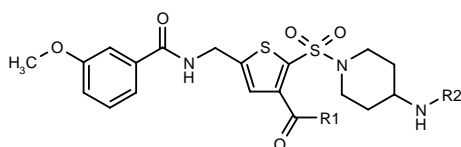
319778

5-(3-Methoxybenzamidoethyl)-2-[4-[3-(trifluoromethylsulfonyl)phenylamino]piperidin-1-ylsulfonyl]thiophene-3-carboxylic acid



C26 H26 F3 N3 O8 S3; Mol wt: 661.6964

ACTION – Water-soluble (0.18 mg/ml at room temperature and pH 7.4) agent that inhibits Jun kinases (JNK), particularly JNK3 (IC₅₀ < 0.1 μM). Potentially useful for the treatment of neuronal disorders such as epilepsy, Alzheimer's disease, Huntington's disease and Parkinson's disease, head and spinal cord injury, multiple sclerosis and ischemia, autoimmune disorders selected from inflammatory bowel disease, rheumatoid arthritis, asthma, septic shock and transplant rejection, retinal diseases, cancer, and also cardiovascular disorders including stroke, arteriosclerosis, myocardial infarction, myocardial reperfusion injury, renal failure and ischemic conditions. Other exemplified compounds are:



Compound	R1	R2	Formula
319781	OH	4-CF ₃ -PhCH ₂	C ₂₇ H ₂₈ F ₃ N ₃ O ₆ S ₂
319785	NHNH ₂	3-(CF ₃ S)-Ph	C ₂₆ H ₂₈ F ₃ N ₅ O ₅ S ₃

SOURCE – Applied Research Systems.

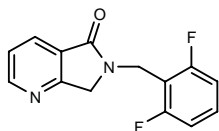
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AWD-47-222*

318144

6-(2,6-Difluorobenzyl)-6,7-dihydro-5H-pyrrolo[3,4-b]-pyridin-5-one



C₁₄ H₁₀ F₂ N₂ O; Mol wt: 260.2420

ACTION – Antiepileptic agent able to protect rats against electrically induced seizures (ED₅₀ = 5.0 mg/kg p.o.) and corneal kindled rats (ED₅₀ = 28.8 mg/kg p.o.). No neurotoxicity was seen at high doses, and the TD₅₀ was > 250 mg/kg p.o. in the rat rotarod test.

SOURCE – AWD.pharma.

REFERENCES

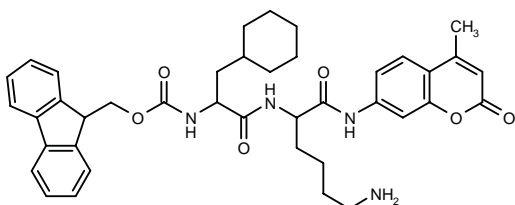
1. Unverferth, K. et al. (Arzneimittelwerk Dresden GmbH) *6,7-Dihydro-pyrrolo[3,4-b]-pyridin-5-ones with an anticonvulsive action and methods for producing the same*. DE 10042093, WO 0218381.
2. Lankau, H.-J. et al. *Synthesis and anticonvulsant activity of AWD 47-222*. 28th Natl Med Chem Symp (June 8-12, San Diego) 2002, Abst 21.

*Identified compound **318144** Drug Data Rep 2002, 024(05): 0406.

GALNON

320704

3-Cyclohexyl-N-(9H-fluoren-9-ylmethoxycarbonyl)-D,L-alanyl-D,L-lysine N-(4-methyl-2-oxo-2H-1-benzopyran-7-yl)amide



C₄₀ H₄₆ N₄ O₆; Mol wt: 678.8254

ACTION – Nonpeptide galanin receptor agonist (K_i = 2.9 and 4.8 μM for galanin receptors in Bowes cells and rat ventral hippocampus, respectively) able to inhibit both basal and forskolin-stimulated adenylate cyclase activity in rat hippocampus (EC₅₀ = 8.0 and 10 μM, respectively). *In vivo*, a dose of 2 mg/kg i.p. protected mice from seizures induced by pentylenetetrazol and reversed the proconvulsant effect of the galanin receptor antagonist M35. Moreover, intrahippocampal injection of compound shortened the duration of selfsustaining status epilepticus in rats. Potentially useful as an antiepileptic agent.

SOURCE – AstraZeneca.

REFERENCES

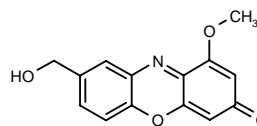
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TREATMENT OF EXTRAPYRAMIDAL MOVEMENT DISORDERS

HALXAZONE

320620

8-(Hydroxymethyl)-1-methoxy-3H-phenoxazin-3-one



C₁₄ H₁₁ N O₄; Mol wt: 257.2439

ACTION – Neuroprotective agent produced by the actinomycete *Streptomyces halstedii* 4029-SVS1, able to protect PC-12 cells from L-DOPA toxicity with an EC₅₀ of 15.4 nM, as well as to protect N18-RE-105 cells from L-glutamate toxicity (EC₅₀ = 19.1 nM). Potentially useful for the treatment of neurodegenerative diseases such as Parkinson's disease.

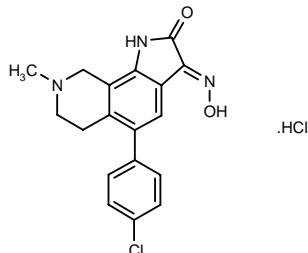
SOURCE – University of Tokyo, Tokyo (JP).

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1. Katoh, H. et al. *A novel neuronal cell protecting substance, halxazone, produced by Streptomyces halstedii*. J Antibiot 2002, 55(5): 508.

NS-417**310280**

5-(4-Chlorophenyl)-8-methyl-2,3,6,7,8,9-hexahydro-1*H*-pyrrolo[3,2-*h*]isoquinoline-2,3-dione 3-oxime hydrochloride



C₁₈ H₁₆ Cl N₃ O₂ · HCl; Mol wt: 378.2573

ACTION – Small molecule with neurotrophic-like activity, shown to concentration-dependently prevent the death of PC-12 cells induced by withdrawal of serum and nerve growth factor (NGF), with a maximal effect at 2-5 μ M. Compound also preserved neurites of differentiated PC-12 cells and significantly potentiated the increase in neurite outgrowth induced by NGF and other growth factors in undifferentiated pheochromocytoma cells. Compound enhanced long-term activation of extracellular regulated kinase (ERK) and Akt kinase induced by NGF and also increased survival of rat dopaminergic cells. Potentially useful for the treatment of neurodegenerative diseases such as Parkinson's disease.

SOURCE – NeuroSearch.

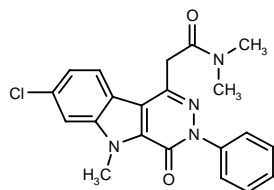
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TREATMENT OF NEURODEGENERATIVE DISEASES

SSR-180575**305858**

2-(7-Chloro-5-methyl-4-oxo-3-phenyl-4,5-dihydro-3*H*-pyridazino[4,5-*b*]indol-1-yl)-*N,N*-dimethylacetamide



C₂₁ H₁₉ Cl N₄ O₂; Mol wt: 394.8601

ACTION – High-affinity ligand for human peripheral benzodiazepine receptors (PBR; IC₅₀ = 2.5-3.5 nM) able to strongly inhibit the *in vivo* binding of [³H]-alpidem to PBR in rat brain and spleen after oral or i.p. administration (ID₅₀ = 0.1-0.3 mg/kg). In an experimental model of motoneuron degeneration induced by facial nerve axotomy in immature rats, compound (6-10 mg/kg p.o. b.i.d. for 8 days) increased survival of facial motoneurons by 40-72% and increased the number of motoneurons immunoreactive to peripherin, the expression of which is upregulated during nerve degeneration, by 87%. In rats, it also improved functional recovery in acrylamide-induced neuropathy (2.5-10 mg/kg p.o.) and of the blink reflex after local injury of the facial nerve. It increased pregnenolone accumulation in rat brain and sciatic nerve, indicating that its neuroprotective effect is steroid-mediated. Potentially useful for the treatment of neurodegenerative diseases such as peripheral neuropathies and amyotrophic lateral sclerosis.

SOURCE – Sanofi-Synthélabo.

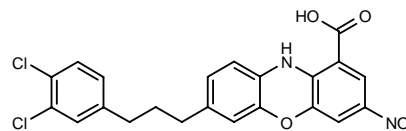
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TREATMENT OF COGNITION DISORDERS

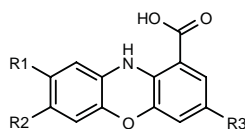
319701

7-[3-(3,4-Dichlorophenyl)propyl]-3-nitro-10*H*-phenoxazine-1-carboxylic acid



C₂₂ H₁₆ Cl₂ N₂ O₅; Mol wt: 459.2834

ACTION – Agent with the ability to inhibit the aggregation of amyloid proteins, expected to be useful for the diagnosis and treatment of Alzheimer's disease. Other exemplified phenoxazine derivatives are:



Compound	R1	R2	R3	Formula
319702		-CH=CHCH=CH-	NO2	C ₁₇ H ₁₀ N ₂ O ₅
319703	Ph	H	NO2	C ₁₉ H ₁₂ N ₂ O ₅
319704	H	3,4-(Cl)2-PhCH2CH2	NO2	C ₂₁ H ₁₄ Cl ₂ N ₂ O ₅
319706	H	3,4-(Cl)2-PhCOCH=CH	NO2	C ₂₂ H ₁₂ Cl ₂ N ₂ O ₆
319707	H	3,4-(Cl)2-PhCH(OH)CH2CH2	NO2	C ₂₂ H ₁₆ Cl ₂ N ₂ O ₆
319708	H	H	NO2	C ₁₃ H ₈ N ₂ O ₅
319710	H	H	OCH2Ph	C ₂₀ H ₁₅ NO ₄

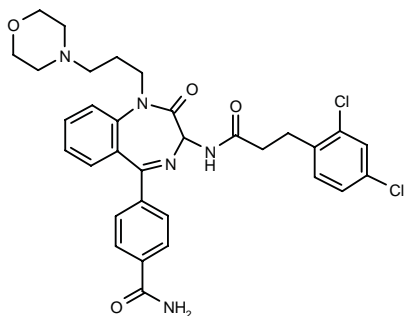
SOURCE – Pfizer.

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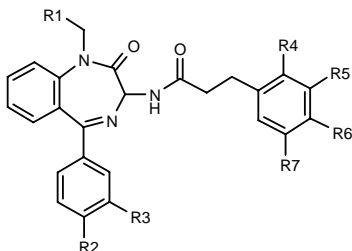
320373

4-[3-[3-(2,4-Dichlorophenyl)propionamido]-1-[3-(4-morpholinyl)propyl]-2-oxo-2,3-dihydro-1*H*-1,4-benzodiazepin-5-yl]benzamide



C₃₂H₃₃Cl₂N₅O₄; Mol wt: 622.5497

ACTION – γ -Secretase inhibitor with potential for interfering with the formation of β -amyloid deposits. Potentially useful for the treatment of Alzheimer's disease. Other specifically claimed benzodiazepine derivatives are:



Compound	R1	R2	R3	R4	R5	R6	R7	Formula
320374	4-MeO-Ph	CONH2	H	Cl	H	Cl	H	C ₃₃ H ₂₈ Cl ₂ N ₄ O ₄
320376	H	-CONHCH2-	Cl	H	Cl	H	H	C ₂₇ H ₂₂ Cl ₂ N ₄ O ₃
320377	H	CONH2	H	H	F	F	H	C ₂₆ H ₂₂ F ₂ N ₄ O ₃
320378	H	CONH2	H	H	H	Cl	H	C ₂₆ H ₂₃ ClN ₄ O ₃
320379	H	CONH2	H	Cl	Cl	H	H	C ₂₆ H ₂₂ Cl ₂ N ₄ O ₃
320380	H	CONH2	H	H	Cl	H	Cl	C ₂₆ H ₂₂ Cl ₂ N ₄ O ₃
320381	H	CONH2	H	H	H	Me	H	C ₂₇ H ₂₆ N ₄ O ₃
320382	H	CONH2	H	Cl	H	H	Cl	C ₂₆ H ₂₂ Cl ₂ N ₄ O ₃

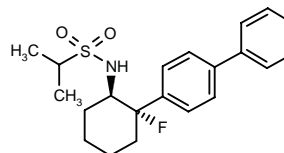
SOURCE – Merck Sharp & Dohme.

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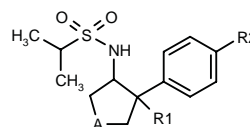
320622

trans-*N*-[2-(Biphenyl-4-yl)-2-fluorocyclohexyl]propane-2-sulfonamide

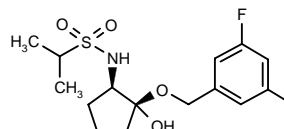


C₂₁H₂₆F N O₂ S; Mol wt: 375.5054

ACTION – A potentiator of glutamate receptor function, potentially useful for the treatment of cognitive and neurodegenerative disorders such as Alzheimer's disease, age-related dementia, age-induced memory impairment, movement disorders, depression, attention deficit hyperactivity disorder, psychosis and stroke, and for reversal of drug-induced states. Other specifically claimed *N*-cycloalkylsulfonamide derivatives are:



Compound	R1	R2	A	Isomer	Formula
320623	F	4-(MeSO2NHCH2CH2)-Ph	-(CH2)2-		C ₂₄ H ₃₃ FN ₂ O ₄ S ₂
320626	OH	OCH2CH2NHAc	-CH2-		C ₁₈ H ₂₈ N ₂ O ₅ S
320627	OH	F	-(CH2)2-		C ₁₅ H ₂₂ FN ₂ O ₃ S
320628	OH	OPh	-(CH2)2-	trans	C ₂₁ H ₂₇ NO ₄ S
320629	OH	i-PrSO2NHCH2CH2O	-(CH2)2-		C ₂₀ H ₃₄ N ₂ O ₆ S ₂
320631	OH	2-CN-PhCH2O	-(CH2)2-		C ₂₃ H ₂₈ N ₂ O ₄ S
320632	F	2-CN-PhCH2O	-(CH2)2-	cis	C ₂₃ H ₂₇ FN ₂ O ₃ S



320625: C₁₅H₂₁F₂N₂O₄S

SOURCE – Lilly.

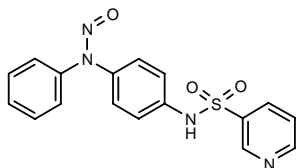
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TREATMENT OF CEREBROVASCULAR DISEASES

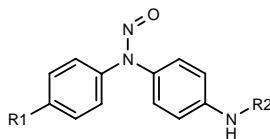
319690

N-[4-(*N*-Nitroso-*N*-phenylamino)phenyl]pyridine-3-sulfonamide



C₁₇H₁₄N₄O₃S; Mol wt: 354.3886

ACTION – Nitric oxide (NO) donor and free radical scavenger for use in the treatment of conditions associated with oxidative stress and lack of availability of NO. Such conditions include atherosclerosis-related ischemia, postangioplasty restenosis, stenosis following vascular surgery, diabetes and insulin resistance, diabetic retinopathy, male erectile dysfunction, cerebral hypoxia, transplant rejection and articular pathologies. Other exemplified *N*-nitroso-*N,N*-diphenylamine derivatives are:



Compound	R1	R2	Formula
319694	H	SO ₂ Ph	C ₁₈ H ₁₅ N ₃ O ₃ S
319696	OMe	3-Pyr-CO	C ₁₉ H ₁₆ N ₄ O ₃
319697	OMe	4-MeO-PhSO ₂	C ₂₀ H ₁₉ N ₃ O ₅ S
319698	OMe	3-NO ₂ -PhCO	C ₂₀ H ₁₆ N ₄ O ₅

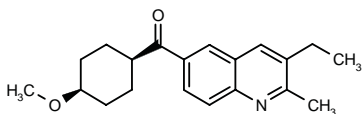
SOURCE – Merck KGaA.

REFERENCES

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319742

cis-1-(3-Ethyl-2-methylquinolin-6-yl)-1-(4-methoxycyclohexyl)methanone



C₂₀H₂₅N O₂; Mol wt: 311.4225

ACTION – Metabotropic glutamate receptor antagonist giving a pIC₅₀ of 8.527 when tested in mGluR₁ (mglu₁)-transfected CHO cells. In addition, it demonstrated *in vivo* antagonist activity in the rat cold allodynia test at a dose of 2.5 mg/kg i.p. Potentially useful for the treatment of CNS disorders including drug abuse, hypoxic, anoxic and ischemic injuries, pain, hypoglycemia, diseases related to neuronal damage, head and spinal cord trauma, myelopathy, dementia, anxiety, schizophrenia, depression, impaired cognition, amnesia, bipolar disorders, conduct disorders, Alzheimer's disease, vascular dementia, Lewy body disease, Parkinson's disease, Huntington's disease, Down's syndrome, epilepsy, aging, amyotrophic lateral sclerosis, multiple sclerosis and AIDS.

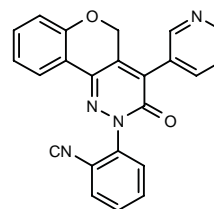
SOURCE – Janssen.

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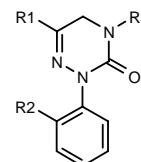
319825

2-[3-Oxo-4-(3-pyridyl)-3,5-dihydro-2*H*-1-benzopyran-[4,3-*c*]pyridazin-2-yl]benzonitrile

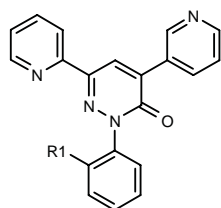


C₂₃H₁₄N₄O₂; Mol wt: 378.3896

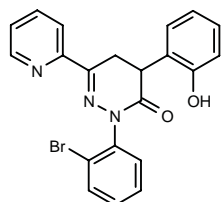
ACTION – Agent that acts as antagonist at AMPA and/or kainate receptors, proven to inhibit AMPA-induced calcium influx in rat cortical neurons with an IC₅₀ of 0.02 μM. *In vivo*, compound prevented AMPA-stimulated twitching at 25 mg/kg p.o. in mice. Potentially useful for the treatment of acute and chronic neurodegenerative disorders including subarachnoid hemorrhage, head and spinal cord trauma, hypoxia, hypoglycemia, Alzheimer's disease, Parkinson's disease, Huntington's chorea and amyotrophic lateral sclerosis. Other exemplified compounds within this series of pyridazinones and 1,2,4-triazinones are:



Compound	R1	R2	R3	Formula
319830	2-Pyr	Br	Ph	C ₂₀ H ₁₅ BrN ₄ O
319831	2-MeO-Ph	CN	Ph	C ₂₃ H ₁₈ N ₄ O ₂
319833	2-Pyr	CN	Ph	C ₂₁ H ₁₅ N ₅ O
319834	2-Pyr	CN	2-Pyr	C ₂₀ H ₁₄ N ₆ O
319835	2-Pyr	CN	3-Pyr	C ₂₀ H ₁₄ N ₆ O



Compound	R1	Formula
319827	CN	C ₂₁ H ₁₃ N ₅ O
319828	H	C ₂₀ H ₁₄ N ₄ O



319826: C₂₁ H₁₆ Br N₃ O₂

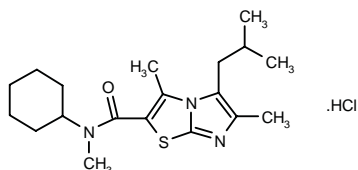
SOURCE – Eisai.

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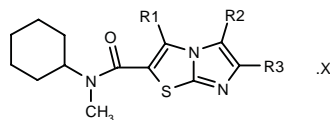
320889

N-Cyclohexyl-5-isobutyl-*N*,3,6-trimethylimidazo[2,1-*b*]-thiazole-2-carboxamide hydrochloride

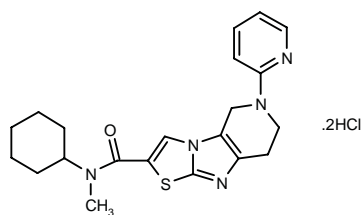


C₁₉ H₂₉ N₃ O S . HCl; Mol wt: 383.9850

ACTION – Agent with the ability to modulate metabotropic glutamate receptors, particularly mGluR₁ (mglu₁) receptors, expected to be useful for the treatment of cerebral infarction. Other exemplified imidazothiazole derivatives are:



Compound	R1	R2	R3	X	Formula
320891	Me	2-thienyl	H	HCl	C ₁₈ H ₂₁ N ₃ OS ₂ .HCl
320892	Me	H	CH ₂ CH ₂ NH ₂	2HCl	C ₁₆ H ₂₄ N ₄ OS.2HCl
320893	Me	CH(NHET)C(Me)=CH ₂	Me	2HCl	C ₂₁ H ₃₂ N ₄ OS.2HCl
320894	Me	CH=CHCO ₂ Me	H	HCl	C ₁₈ H ₂₃ N ₃ O ₃ S.HCl
320895	Me	CH=C(Me)CH ₂ OH	Me		C ₁₉ H ₂₇ N ₃ O ₂ S
320896	Me	CH=C(Me)CH ₂ -N(Me)CH ₂ CH ₂ OMe	H	2HCl	C ₂₂ H ₃₄ N ₄ O ₂ S.2HCl
320897	H	cyclohexylidene=CH	H	HCl	C ₂₀ H ₂₇ N ₃ OS.HCl



320898: C₂₁ H₂₅ N₅ O S . 2HCl

SOURCE – Yamanouchi.

REFERENCES

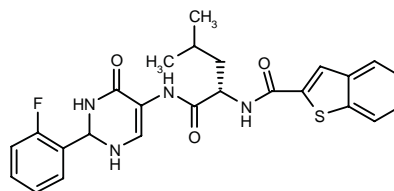
1. Hayashibe, S. et al. (Yamanouchi Pharmaceutical Co., Ltd.) *Novel imidazothiazole derivs*. JP 2002105085.

MISCELLANEOUS NEUROLOGIC DRUGS

NPI-3493

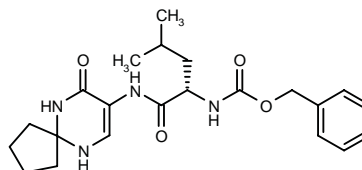
320726

*N*²-(1-Benzothien-2-ylcarbonyl)-*N*¹-[2-(2-fluorophenyl)-4-oxo-1,2,3,4-tetrahydropyrimidin-5-yl]-L-leucinamide



C₂₅ H₂₅ F N₄ O₃ S; Mol wt: 480.5615

ACTION – Cysteine protease inhibitor proven to inhibit cathepsins B, L, K and S *in vitro* with respective IC₅₀ values of 0.42, 0.17, 0.014 and 0.037 μM. In addition, it demonstrated favorable pharmacokinetics in rodents following administration at a dose of 5 mg/kg, with an oral bioavailability of 60-70%. Potentially useful for the treatment of muscular dystrophy, osteoporosis, cancer, rheumatoid arthritis, neuronal or cardiac ischemia, allergic immune responses and protozoal or bacterial infections. Another exemplified dihydropyrimidine derivative is:



NPI-3469 [320727]: C₂₂ H₃₀ N₄ O₄

SOURCE – Naeja.

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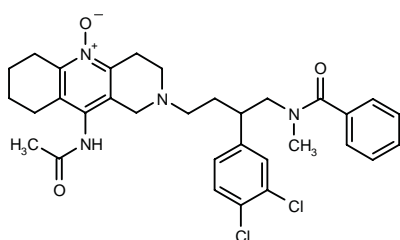
1. Singh, R. et al. (Naeja Pharmaceuticals Inc.) *Dihydropyrimidine derivs. as cysteine protease inhibitors*. WO 0232879.

RESPIRATORY DRUGS

ASTHMA THERAPY

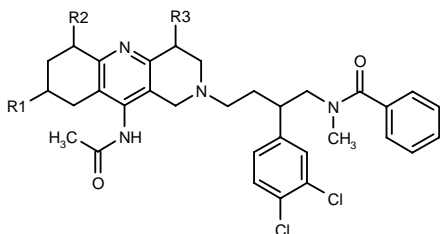
319989

N-[4-(10-Acetamido-5-oxido-1,2,3,4,6,7,8,9-octahydrobenzo[*b*]-1,6-naphthyridin-2-yl)-2-(3,4-dichlorophenyl)-butyl]-*N*-methylbenzamide



C32 H36 Cl2 N4 O3; Mol wt: 595.5674

ACTION – Tachykinin NK₂ antagonist, proven to inhibit Nle10-NKA(4-10)-stimulated contractions in pig tracheal preparations with a pA₂ of 10.3. Potentially useful for the treatment of asthma, bronchitis, pollakiuria, urinary incontinence, colitis and irritable bowel syndrome. Other exemplified naphthyridine derivatives are:



Compound	R1	R2	R3	Formula
319990	H	H	OAc	C ₃₄ H ₃₆ Cl ₂ N ₄ O ₄
319991	H	OAc	H	C ₃₄ H ₃₆ Cl ₂ N ₄ O ₄
319992	H	H	OH	C ₃₂ H ₃₆ Cl ₂ N ₄ O ₃
319993	H	OH	H	C ₃₂ H ₃₆ Cl ₂ N ₄ O ₃
319994	OH	H	H	C ₃₂ H ₃₆ Cl ₂ N ₄ O ₃

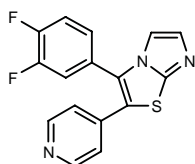
SOURCE – Nippon Kayaku.

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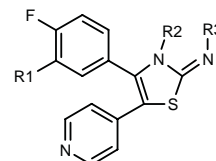
320003

3-(3,4-Difluorophenyl)-2-(4-pyridyl)imidazo[2,1-*b*]thiazole



C16 H9 F2 N3 S; Mol wt: 313.3301

ACTION – TNF- α production inhibitor, as demonstrated both *in vitro* (IC₅₀ = 11 μ M in rat blood cells) and *in vivo* in rats (94% inhibition at 10 mg/kg p.o.). In addition, no deaths or anomalies were observed in acute toxicity tests in mice following oral administration at 10 mg/kg/day for 14 days. Potentially useful for the treatment of allergy, chronic rheumatoid arthritis and ulcerative colitis, as well as other TNF- α -mediated disorders such as bronchial asthma, septic shock, inflammatory bowel disease, inflammation of organs, bone resorption diseases, diabetes, psoriasis, Crohn's disease, malaria, inflammatory pulmonary disease, thrombosis and AIDS. Other exemplified thiazole-containing bicyclic compounds are:



Compound	R1	R2,R3	Formula
320004	H	-CH=CH-	C ₁₆ H ₁₀ FN ₃ S
320006	H	-N=CH-	C ₁₅ H ₉ FN ₄ S
320007	H	-CONHCO-	C ₁₆ H ₉ FN ₄ O ₂ S
320008	H	-CON=C(Me)-	C ₁₇ H ₁₃ FN ₄ OS
320009	H	-COCH=CH-	C ₁₇ H ₁₀ FN ₃ OS
320010	H	-CH(Me)CO-	C ₁₇ H ₁₂ FN ₃ OS
320011	F	-CH(Me)CO-	C ₁₇ H ₁₁ F ₂ N ₃ OS

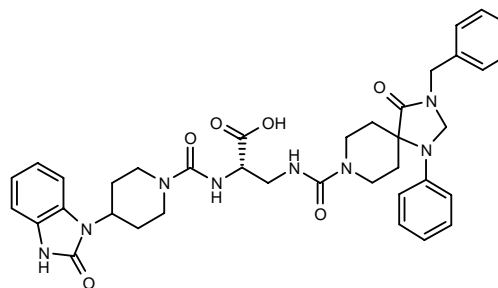
SOURCE – Nikken Chemicals.

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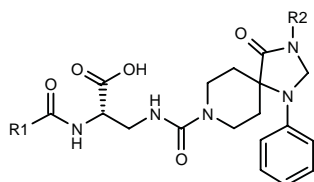
320012

3-(3-Benzyl-4-oxo-1-phenyl-1,3,8-triazaspiro[4.5]dec-8-ylcarboxamido)-2(*S*)-[4-(2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl)piperidin-1-ylcarboxamido]propionic acid



C37 H42 N8 O6; Mol wt: 694.7888

ACTION – An inhibitor of VLA-4-mediated cell adhesion shown to inhibit the binding of CS-1 peptide to a VLA-4-IgG chimeric protein with an IC₅₀ of 0.98 nM. Potentially useful for the treatment of allergic inflammatory diseases including bronchial asthma, atopic dermatitis and allergic rhinitis, autoimmune diseases such as hepatitis, nephritis, rheumatoid arthritis and multiple sclerosis, and also transplant rejection, type 1 diabetes, Crohn's disease, ulcerative colitis, restenosis and arteriosclerosis. Other exemplified spiro compounds are:



Compound	R1	R2	Formula
320013	2,6-(Cl)2-Ph	H	C ₂₄ H ₂₅ Cl ₂ N ₅ O ₅
320014	2,6-(MeO)2-Ph	CH ₂ Ph	C ₃₃ H ₃₇ N ₅ O ₇
320015	2,6-(Me)2-Ph	CH ₂ Ph	C ₃₃ H ₃₇ N ₅ O ₅
320016	4-(i-PrCONH)-4-Ph-1-Pip	CH ₂ Ph	C ₄₀ H ₄₉ N ₇ O ₆

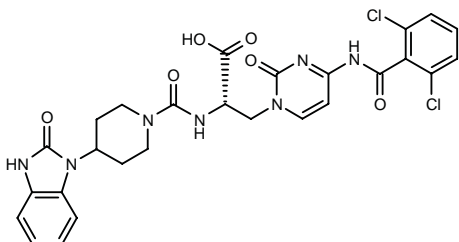
SOURCE – Toray.

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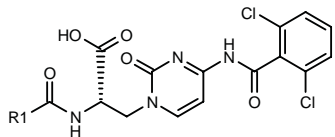
320036

3-[4-(2,6-Dichlorobenzamido)-2-oxo-1,2-dihydropyrimidin-1-yl]-2(S)-[4-(2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)piperidin-1-ylcarboxamido]propionic acid



C₂₇ H₂₅ Cl₂ N₇ O₆; Mol wt: 614.4435

ACTION – An inhibitor of VLA-4-mediated cell adhesion proven to inhibit the binding of CS-1 peptide to VLA-4-IgG chimeric protein with an IC₅₀ of 0.97 nM. Potentially useful for the treatment of allergic disorders such as asthma, atopic dermatitis and allergic rhinitis, autoimmune diseases including hepatitis, nephritis, rheumatoid arthritis and multiple sclerosis. Further applications include transplant rejection, type 1 diabetes, Crohn's disease, ulcerative colitis, arteriosclerosis and postoperative restenosis. Other exemplified urea derivatives are:



Compound	R1	Formula
320038	1-(SO ₂ Me)-spiro[indoline-3,4'-piperidin]-1'-yl	C ₂₈ H ₂₈ Cl ₂ N ₆ O ₇ S
320039	4-oxo-1-Ph-1,3,8-triazaspiro[4.5]dec-8-yl	C ₂₈ H ₂₇ Cl ₂ N ₇ O ₆
320041	4-(AcNH)-4-Ph-1-Pip	C ₂₈ H ₂₈ Cl ₂ N ₆ O ₆
320042	2(R),6(S)-(Me)2-1-Pip	C ₂₂ H ₂₅ Cl ₂ N ₆ O ₅

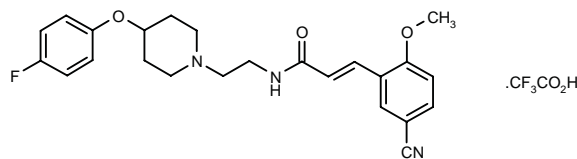
SOURCE – Toray.

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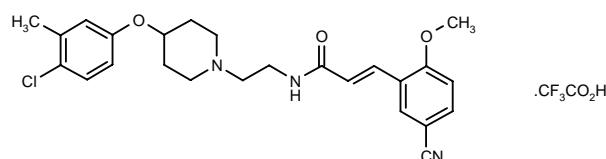
320205

3-(5-Cyano-2-methoxyphenyl)-N-[2-[4-(4-fluorophenoxy)piperidin-1-yl]ethyl]-2(E)-propenamide trifluoroacetate



C₂₄ H₂₆ F N₃ O₃ . C₂ H F₃ O₂; Mol wt: 537.5073

ACTION – Chemokine CCR3 receptor antagonist, potentially useful for the treatment of inflammatory or obstructive airways diseases such as asthma, acute lung injury, adult respiratory distress syndrome, chronic obstructive pulmonary disease, bronchitis, emphysema and pneumoconiosis. Another exemplified cinnamic amide is:



320206: C₂₅ H₂₈ Cl N₃ O₃ . C₂ H F₃ O₂

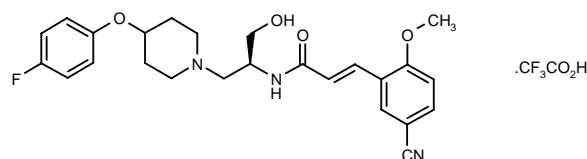
SOURCE – Novartis.

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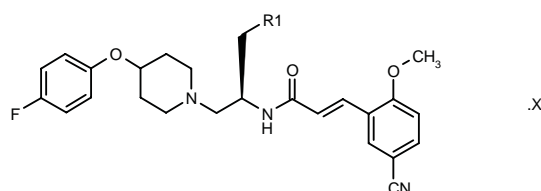
320207

3-(5-Cyano-2-methoxyphenyl)-N-[2-[4-(4-fluorophenoxy)-piperidin-1-yl]-1(S)-(hydroxymethyl)ethyl]-2-propenamide trifluoroacetate



C₂₅ H₂₈ F N₃ O₄ . C₂ H F₃ O₂; Mol wt: 567.5331

ACTION – Chemokine CCR3 receptor antagonist, potentially useful for the treatment of inflammatory or obstructive airways diseases such as asthma, acute lung injury, adult respiratory distress syndrome, chronic obstructive pulmonary disease, bronchitis, emphysema and pneumoconiosis. Other exemplified cinnamic amide are:



Compound	R1	X	Formula
320208	CON(Me)CH ₂ CH ₂ OH	CF ₃ CO ₂ H	C ₂₉ H ₃₅ FN ₄ O ₅ ·C ₂ H ₃ F ₃ O ₂
320209	NHAc		C ₂₇ H ₃₁ FN ₄ O ₄

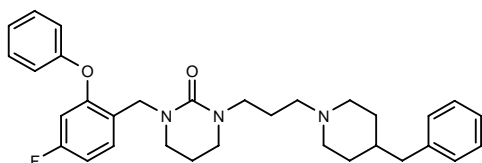
SOURCE – Novartis.

REFERENCES

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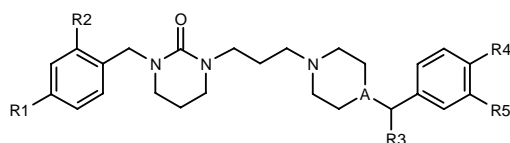
320296

1-[3-(4-Benzylpiperidin-1-yl)propyl]-3-(4-fluoro-2-phenoxybenzyl)perhydropyrimidin-2-one



C₃₂H₃₈F N₃ O₂; Mol wt: 515.6692

ACTION – Chemokine CCR3 receptor antagonist reported to inhibit the eotaxin-stimulated increase in calcium levels in CCR3-transfected cells with an IC₅₀ of 2.1 μM. Potentially useful for the treatment of allergic inflammatory diseases caused by leukocyte accumulation including bronchial asthma, atopic dermatitis, allergic rhinitis, chronic sinusitis, etc. Other exemplified nitrogen-containing compounds are:



Compound	R1	R2	R3	R4	R5	A	Formula
320297	H	Me	Ph	H	H	CH	C ₃₃ H ₄₁ N ₃ O
320298	H	Ph	H	H	H	CH	C ₃₂ H ₃₉ N ₃ O
320299	Me	H	H	H	H	CH	C ₂₇ H ₃₇ N ₃ O
320300	NH ₂	H	Ph	H	H	N	C ₃₁ H ₃₉ N ₅ O
320301	F	OPh	Ph	H	H	N	C ₃₇ H ₄₁ FN ₄ O ₂
320302	Me	H	H	-CH=CHCH=CH-	N	N	C ₃₀ H ₃₈ N ₄ O

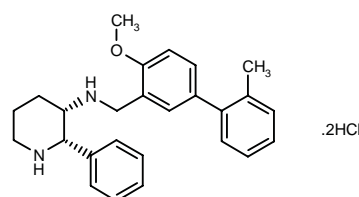
SOURCE – Toray.

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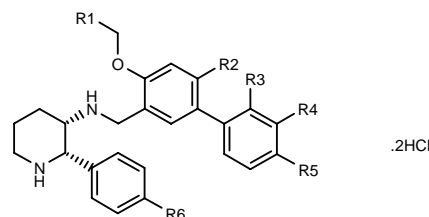
320363

N-(4-Methoxy-2'-methylbiphenyl-3-ylmethyl)-2(*S*)-phenylpiperidin-3(*S*)-amine dihydrochloride



C₂₆ H₃₀ N₂ O . 2HCl; Mol wt: 459.4578

ACTION – Tachykinin antagonist, particularly substance P receptor antagonist, expected to be useful for the treatment of inflammation, allergic diseases, pain, migraine, itching, cough, CNS disorders including schizophrenia, Parkinson's disease, depression, anxiety and dementia, digestive disorders associated with bacterial infections, nausea and vomiting, urinary disorders, cardiovascular diseases and immune disorders. Other exemplified 5-phenylbenzylamine compounds are:



Compound	R1	R2	R3	R4	R5	R6	Formula
320364	H	H	H	CN	H	H	C ₂₈ H ₂₇ N ₃ O·2HCl
320365	H	H	H	H	CF ₃	H	C ₂₈ H ₂₇ F ₃ N ₂ O·2HCl
320366	H	H	F	F	F	H	C ₂₈ H ₂₅ F ₃ N ₂ O·2HCl
320367	H	H	CN	H	F	H	C ₂₈ H ₂₆ FN ₃ O·2HCl
320368	H	H	H	H	Cl	H	C ₂₅ H ₂₆ ClFN ₂ O·2HCl
320369	H	Me	H	H	F	H	C ₂₈ H ₂₉ FN ₂ O·2HCl
320370	H	H	H	H	F	OMe	C ₂₈ H ₂₉ FN ₂ O ₂ ·2HCl
320371	Me	H	H	H	CN	H	C ₂₇ H ₂₉ N ₃ O·2HCl

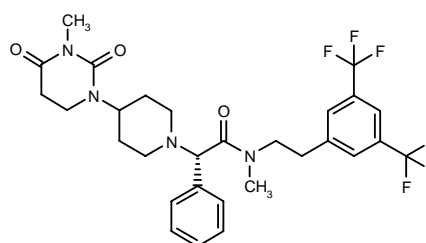
SOURCE – Tanabe Seiyaku.

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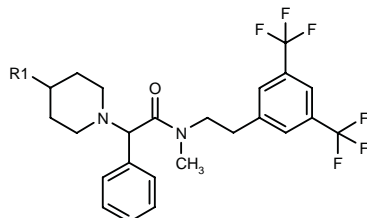
320754

N-[2-[3,5-Bis(trifluoromethyl)phenyl]ethyl]-*N*-methyl-2(*S*)-[4-(3-methyl-2,4-dioxoperhydropyrimidin-1-yl)piperidin-1-yl]-2-phenylacetamide



C₂₉ H₃₂ F₆ N₄ O₃; Mol wt: 598.5848

ACTION – Tachykinin receptor antagonist considered to have potential in the treatment of a broad range of tachykinin-mediated conditions including respiratory disorders (asthma, chronic bronchitis, COPD and cystic fibrosis), eye disorders (conjunctivitis and iritis), skin disorders (contact dermatitis, pruritus, urticaria and psoriasis), gastrointestinal disorders (ulcerative colitis, Crohn's disease and irritable bowel syndrome), arthritis, osteoporosis, and also urinary tract disorders such as urinary incontinence, cystitis or urethritis. Other exemplified compounds are:



Compound	R1	Isomer	Formula
320755	NHCONHMe		C ₂₆ H ₃₀ F ₆ N ₄ O ₂
320757	2-oxo-perhydro-1,3-oxazin-3-yl	S	C ₂₈ H ₃₁ F ₆ N ₃ O ₃
320758	2,4-dioxo-3-oxazolidinyl	S	C ₂₇ H ₂₇ F ₆ N ₃ O ₄
320759	3,6-(Me)2-2,4-dioxo-perhydro-1-pyrimidinyl	S	C ₃₀ H ₃₄ F ₆ N ₄ O ₃
320761	2-oxo-1-imidazolidinyl	S	C ₂₇ H ₃₀ F ₆ N ₄ O ₂
320762	NHCONHPh	S	C ₃₁ H ₃₂ F ₆ N ₄ O ₂

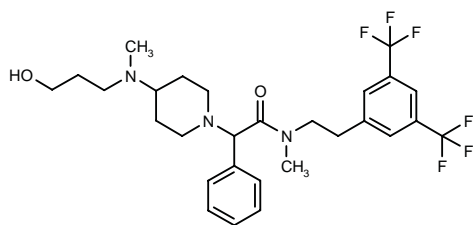
SOURCE – Boehringer Ingelheim.

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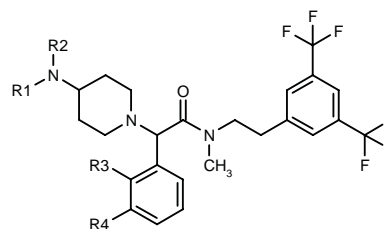
320764

N-[2-[3,5-Bis(trifluoromethyl)phenyl]ethyl]-2-[4-[*N*-(3-hydroxypropyl)-*N*-methylamino]piperidin-1-yl]-*N*-methyl-2-phenylacetamide



C₂₈H₃₅F₆N₃O₂; Mol wt: 559.5915

ACTION – Tachykinin receptor antagonist considered to have potential in the treatment of a broad range of tachykinin-mediated conditions including respiratory disorders (asthma, chronic bronchitis, COPD and cystic fibrosis), eye disorders (conjunctivitis and iritis), skin disorders (contact dermatitis, pruritus, urticaria and psoriasis), gastrointestinal disorders (ulcerative colitis, Crohn's disease and irritable bowel syndrome), arthritis, osteoporosis, and also urinary tract disorders such as urinary incontinence, cystitis or urethritis. Other exemplified compounds are:



Compound	R1	R2	R3	R4	Isomer	Formula
320765	CH2OH	CHCH2OH	H	H		C27H33F6N3O3
320766	Me	cyclopropyl-CH2	H	H		C28H35F6N3O
320767	CH2CH2OH	(CH2)3OH	H	H	S	C29H37F6N3O3
320768	(CH2)3OH	cyclopropyl-CH2	H	H	S	C31H39F6N3O2
320770	Me	(CH2)3OH	-OCH2O-		S	C29H35F6N3O4
320771	CH2CH2OH	(CH2)3OH	-OCH2O-		S	C30H37F6N3O5
320772	H	CH(CH2OH)2	-OCH2O-		S	C28H33F6N3O5

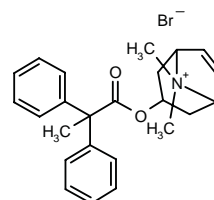
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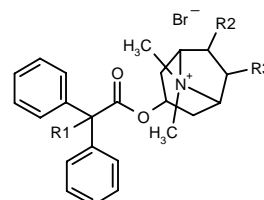
320773

3-(2,2-Diphenylpropionyloxy)-8,8-dimethyl-8-azonia-bicyclo[3.2.1]oct-6-ene bromide



C₂₄H₂₈BrN₂O₂; Mol wt: 442.3942

ACTION – A anticholinergic agent for the treatment of asthma, chronic obstructive pulmonary disease, vagal sinus bradycardia, arrhythmia, gastrointestinal spasms, urinary incontinence and menstrual complaints. Other exemplified compounds are:



Compound	R1	R2,R3	Formula
320776	Me	-O-	C ₂₄ H ₂₆ BrNO ₃
320777	F	-O-	C ₂₃ H ₂₅ BrFNO ₃
320778	F	bond	C ₂₃ H ₂₅ BrFNO ₂

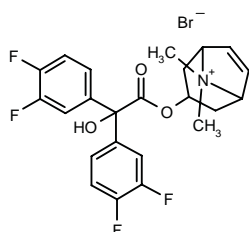
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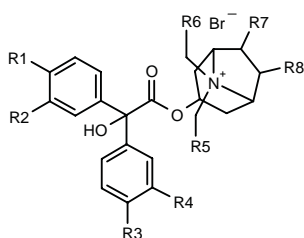
320780

3-[2,2-Bis(3,4-difluorophenyl)-2-hydroxyacetoxy]-8,8-dimethyl-8-azoniabicyclo[3.2.1]oct-6-ene bromide



C₂₃ H₂₂ Br F₄ N O₃; Mol wt: 516.3268

ACTION – A anticholinergic agent for the treatment of asthma, chronic obstructive pulmonary disease, vagal sinus bradycardia, arrhythmia, gastrointestinal spasms, urinary incontinence and menstrual complaints. Other exemplified compounds are:



Compound	R1	R2	R3	R4	R5=R6	R7,R8	Formula
320781	F	F	F	F	H	-O-	C ₂₃ H ₂₂ BrF ₄ NO ₄
320782	Cl	H	Cl	H	H	-O-	C ₂₃ H ₂₄ BrCl ₂ NO ₄
320783	F	H	F	H	H	-O-	C ₂₃ H ₂₄ BrF ₂ NO ₄
320784	H	F	H	F	H	bond	C ₂₃ H ₂₄ BrF ₂ NO ₃
320785	H	F	H	F	H	-O-	C ₂₃ H ₂₄ BrF ₂ NO ₄
320786	F	H	F	H	Me	bond	C ₂₅ H ₂₈ BrF ₂ NO ₃

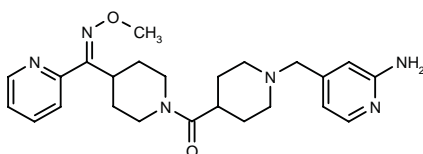
SOURCE – Boehringer Ingelheim.

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320790

1-[1-[1-(2-Aminopyridin-4-ylmethyl)piperidin-4-ylcarbonyl]piperidin-4-yl]-1-(2-pyridyl)methanone O-methyl-oxime



C₂₄ H₃₂ N₆ O₂; Mol wt: 436.5568

ACTION – Histamine H₃ receptor antagonist (K_i = 0.83 nM), expected to be useful for the treatment of allergy, allergy-induced airways responses and nasal congestion, as well as other H₃-mediated conditions including cardiovascular disease, gastrointestinal disorders, obesity, sleep disorders, attention deficit hyperactivity disorder, Alzheimer's disease, schizophrenia and migraine.

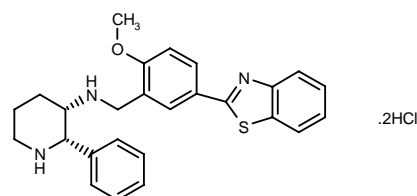
SOURCE – Schering-Plough.

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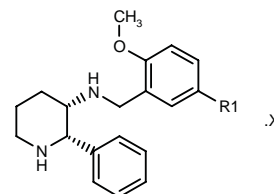
320955

(2S*,3S*)-N-[5-(2-Benzothiazolyl)-2-methoxybenzyl]-2-phenylpiperidin-3-amine dihydrochloride



C₂₆ H₂₇ N₃ O S . 2HCl; Mol wt: 502.5071

ACTION – A tachykinin receptor, particularly substance P receptor, antagonist, potentially useful for the treatment of allergic diseases including atopic dermatitis, herpes, asthma, psoriasis, rhinitis, arthritis, osteoporosis, multiple sclerosis, conjunctivitis and cystitis. Other applications include pain, migraine, cough, itching, CNS disorders such as schizophrenia, Parkinson's disease, depression, anxiety and Alzheimer's disease, digestive disorders including irritable bowel syndrome, ulcerative colitis and Crohn's disease, nausea and vomiting, urinary incontinence and pollakiuria, and circulatory disorders such as angina pectoris, hypertension, heart failure and thrombosis. Other exemplified benzylamine compounds include the following:



Compound	R1	X	Formula
320956	6-Me-4-oxo-3,4-dihydro-3-quinazolinyl	2HCl	C ₂₈ H ₃₀ N ₄ O ₂ .2HCl
320957	6-NO ₂ -4-oxo-3,4-dihydro-3-quinazolinyl	2HCl	C ₂₇ H ₂₇ N ₅ O ₄ .2HCl
320958	1-oxo-1,2-dihydro-2-isoquinolinyl	2HCl	C ₂₈ H ₂₈ N ₃ O ₂ .2HCl
320959	5-F-1-oxo-1,2-dihydro-2-isoquinolinyl		C ₂₈ H ₂₈ FN ₃ O ₂
320960	2-quinoxaliny	2HCl	C ₂₇ H ₂₉ N ₄ O ₂ .2HCl
320961	3-quinolyl	3HCl	C ₂₈ H ₂₉ N ₃ O ₂ .3HCl
320963	6-Cl-2-quinoliny	3HCl	C ₂₈ H ₂₈ ClN ₃ O ₂ .3HCl
320964	4-oxo-4H-1-benzopyran-6-yl	2HCl	C ₂₈ H ₂₈ N ₂ O ₃ .2HCl

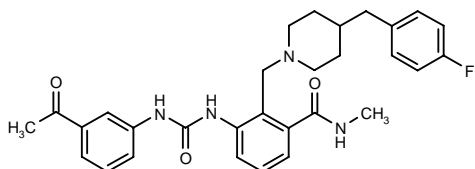
SOURCE – Tanabe Seiyaku.

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320987

3-[3-(3-Acetylphenyl)ureido]-2-[4-(4-fluorobenzyl)-piperidin-1-ylmethyl]-*N*-methylbenzamide



C30 H33 F N4 O3; Mol wt: 516.6137

ACTION – Chemokine CCR3 receptor antagonist (IC_{50} = 1.1 nM) with high selectivity over other chemokine receptors (CCR1, CCR2 and CCR5) and other transmembrane receptors. Potentially useful for the treatment of allergic asthma.

SOURCE – Bristol-Myers Squibb.

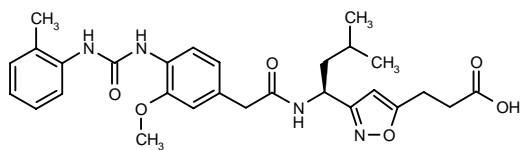
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CP-664511^{*,1-4}

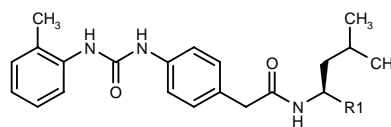
308877

3-[3-[1(*S*)-[2-[3-Methoxy-4-[3-(2-methylphenyl)ureido]-phenyl]acetamido]-3-methylbutyl]isoxazol-5-yl]propionic acid



C28 H34 N4 O6; Mol wt: 522.5986

ACTION – Small-molecule inhibitor of the $\alpha_4\beta_1$ /VCAM-1 interaction proven to inhibit Jurkat cell binding to VCAM-1 with an IC_{50} value of 0.52 nM; its potency was slightly affected by the presence of serum (IC_{50} = 5 nM). In ovalbumin-sensitized mice, compound dose-dependently inhibited antigen-induced pulmonary eosinophilia with an ED_{50} of about 2 μ g following intratracheal instillation; a dose of 10 mg/kg i.p. was also active in this model, giving a 58% reduction in bronchoalveolar lavage (BAL) eosinophil infiltration. Potentially useful for the treatment of asthma and other allergic pulmonary inflammatory disorders. Other related compounds are:



Compound	R1	Formula
CP-609643 ^{*,1-4} [285150]	5-(CO ₂ HCH ₂ CH ₂)-3-isoxazolyl	C ₂₇ H ₃₂ N ₄ O ₅
CP-619700 ^{1,3,4} [305657]	5-(CO ₂ HCH ₂ CH ₂)-2-thiazolyl	C ₂₇ H ₃₂ N ₄ O ₄ S

SOURCE – Pfizer.

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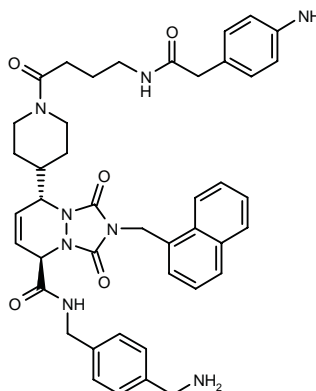
*Identified compound **308877** Drug Data Rep 2001, 023(11): 1059.

Identified compound **285150 (see **285147**) Drug Data Rep 2000, 022(04): 0323.

MOL-6131

289946

N-[4-(Aminomethyl)benzyl]-8(*S*)-[1-[4-[2-(4-aminophenyl)-acetamido]butyl]piperidin-4-yl]-2-(naphthalen-1-ylmethyl)-1,3-dioxo-2,3,5,8-tetrahydro-1*H*-[1,2,4]triazolo[1,2-*a*]pyridazine-5(*R*)-carboxamide



C43 H48 N8 O5; Mol wt: 756.9032

ACTION – Potent and selective, nonpeptide inhibitor of human lung mast cell tryptase ($K_i = 45$ nM) with high selectivity over trypsin ($K_i = 1061$ nM), thrombin ($K_i = 23,640$ nM) and other serine proteases ($K_i = > 40,000$ nM). In antigen-sensitized mice, compound blocked antigen-induced airways inflammation, as measured by eosinophil influx into the bronchoalveolar lavage fluid (BALF); it was more effective after intranasal than after oral administration (65.1% inhibition at 10 mg/kg i.n. and 41% inhibition at 25 mg/kg p.o.). Compound also significantly reduced the total number of inflammatory cells and neutrophils in lung tissue, goblet cell hyperplasia, mucus secretion and airways edema, but it had no significant effect on the antigen-induced airways hyperreactivity to methacholine. Compound significantly reduced the levels of IL-4 and IL-13 in BALF and VCAM-1 expression in pulmonary endothelial cells. Potentially useful for the treatment of asthma.

SOURCES – Choongwae; Molecumetics.

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TREATMENT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASES

TIOTROPIUM BROMIDE⁺

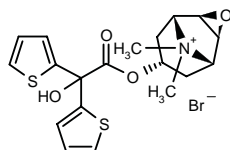
Prop INN

193167

(1*R*,2*R*,4*S*,5*S*,7*S*)-7-[2-Hydroxy-2,2-di(2-thienyl)acetoxy]-9,9-dimethyl-3-oxa-9-azoniatricyclo[3.3.1.0^{2,4}]nonane bromide

6β,7β-Epoxy-3α-[2-hydroxy-2,2-di(2-thienyl)acetoxy]-8,8-dimethyl-1α*H*,5α*H*-tropanium bromide

BA-679-BR



C19 H22 Br N O4 S2; Mol wt: 472.4230

ACTION – Bronchodilator, a muscarinic M_3 receptor antagonist.

INDICATION – Maintenance treatment of patients with chronic obstructive pulmonary diseases (COPD), including chronic bronchitis and emphysema.

PRESENTATION – Inhalation powder in capsules, 22.5 μg tiotropium bromide monohydrate equivalent to 18 μg tiotropium.

PROPRIETARY NAME – Spiriva (NL, PH).

SOURCES – Boehringer Ingelheim; Pfizer.

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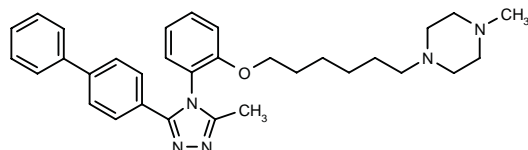
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CARDIOVASCULAR DRUGS

ANTIHYPERTENSIVE DRUGS

319376

1-[6-[2-[3-(4-Biphenyl)-5-methyl-4H-1,2,4-triazol-4-yl]phenoxy]hexyl]-4-methylpiperazine



C32 H39 N5 O; Mol wt: 509.6941

ACTION – Selective human vasopressin V_{1a} receptor antagonist with high affinity for the human receptor ($K_i = 1.04$ nM) and excellent selectivity over human V_2 receptors ($K_i = 1780$). It also exhibited high affinity and selectivity for rat V_{1a} over V_2 receptors ($K_i = 17.3$ and 1240 nM, respectively). *In vivo*, compound dose-dependently antagonized the arginine vasopressin (AVP)-induced increase in diastolic blood pressure in pithed rats with an ID_{50} of 0.695 mg/kg i.v.; good efficacy was also seen following a dose of 10 mg/kg p.o., which produced a long-lasting (8 h) effect. Compound did not affect urine volume even at the highest dose tested (100 mg/kg). Potentially useful for the treatment of hypertension.

SOURCE – Yamanouchi.

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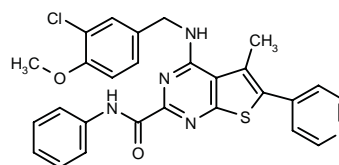
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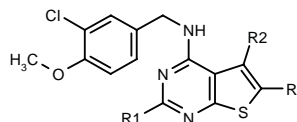
320286

4-(3-Chloro-4-methoxybenzylamino)-5-methyl-N-phenyl-6-(4-pyridyl)thieno[2,3-d]pyrimidine-2-carboxamide



C27 H22 Cl N5 O2 S; Mol wt: 516.0228

ACTION – cGMP-specific phosphodiesterase (PDE) inhibitor giving an IC_{50} of 0.27 nM against PDE5 and exhibiting > 37,000-, > 8,800- and > 37,000-fold selectivity versus PDE1, PDE3 and PDE4, respectively. Potentially useful as a vasodilator for the treatment of hypertension, heart failure, myocardial infarction, angina pectoris, arteriosclerosis, postangioplasty restenosis, cardiac edema, pulmonary hypertension, renal failure, renal edema, hepatic edema, asthma, bronchitis, dementia, immunodeficiency, glaucoma and impotence, among other PDE-related disorders. Other exemplified thienopyrimidine compounds are:



Compound	R1	R2	R3	Formula
320287	4-Pyr	Me	CO2H	C ₂₁ H ₁₇ ClN ₄ O ₃ S
320288	4-Pyr	Me	CO2Et	C ₂₃ H ₂₁ ClN ₄ O ₃ S
320289	CONHPh	Me	4-F-Ph	C ₂₈ H ₂₂ ClFN ₄ O ₂ S
320290	CONHPh	Me	H	C ₂₂ H ₁₉ ClN ₄ O ₂ S
320291	CO2H	H	Ph	C ₂₁ H ₁₆ ClN ₃ O ₃ S
320292	CO2Et	H	Ph	C ₂₃ H ₂₀ ClN ₃ O ₃ S
320294	CONHPh	H	Ph	C ₂₇ H ₂₁ ClN ₄ O ₂ S

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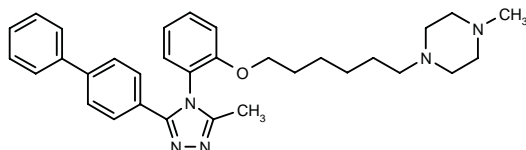
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CARDIOVASCULAR DRUGS

ANTIHYPERTENSIVE DRUGS

319376

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SOURCE – Yamanouchi.

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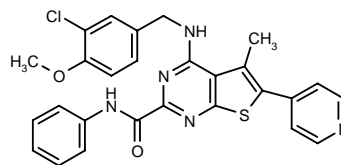
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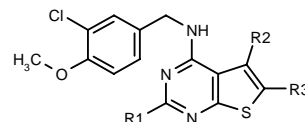
320286

4-(3-Chloro-4-methoxybenzylamino)-5-methyl-N-phenyl-6-(4-pyridyl)thieno[2,3-d]pyrimidine-2-carboxamide



C27 H22 Cl N5 O2 S; Mol wt: 516.0228

ACTION – cGMP-specific phosphodiesterase (PDE) inhibitor giving an IC_{50} of 0.27 nM against PDE5 and exhibiting > 37,000-, > 8,800- and > 37,000-fold selectivity versus PDE1, PDE3 and PDE4, respectively. Potentially useful as a vasodilator for the treatment of hypertension, heart failure, myocardial infarction, angina pectoris, arteriosclerosis, postangioplasty restenosis, cardiac edema, pulmonary hypertension, renal failure, renal edema, hepatic edema, asthma, bronchitis, dementia, immunodeficiency, glaucoma and impotence, among other PDE-related disorders. Other exemplified thienopyrimidine compounds are:



Compound	R1	R2	R3	Formula
320287	4-Pyr	Me	CO2H	C ₂₁ H ₁₇ ClN ₄ O ₃ S
320288	4-Pyr	Me	CO2Et	C ₂₃ H ₂₁ ClN ₄ O ₃ S
320289	CONHPh	Me	4-F-Ph	C ₂₈ H ₂₂ ClFN ₄ O ₂ S
320290	CONHPh	Me	H	C ₂₂ H ₁₉ ClN ₄ O ₂ S
320291	CO2H	H	Ph	C ₂₁ H ₁₆ ClN ₃ O ₃ S
320292	CO2Et	H	Ph	C ₂₃ H ₂₀ ClN ₃ O ₃ S
320294	CONHPh	H	Ph	C ₂₇ H ₂₁ ClN ₄ O ₂ S

SOURCE – Nippon Soda.

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TREPROSTINIL SODIUM

USAN

157437

9-Deoxy-3,7-(1',3'-interphenylene)-2',9-methano-3-oxa-4,5,6-trinor-13,14-dihydroprostaglandin F1 sodium salt

(1*R*,2*R*,3*aS*,9*aS*)-2-[2-Hydroxy-1-[3(*S*)-hydroxyoctyl]-2,3,3*a*,4,9,9*a*-hexahydro-1*H*-benz[*f*]inden-5-yloxy]acetic acid sodium salt

BW-15AU

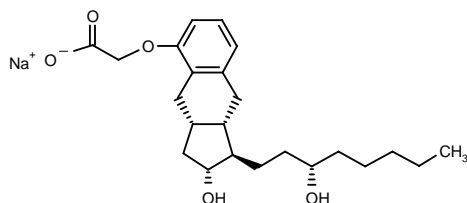
LRX-15

U-62840

15AU81⁺

UT-15

Uniprost



C23 H33 Na O5; Mol wt: 412.4987

ACTION – Prostacyclin analogue that exerts vasodilating and antiplatelet effects.

INDICATION – Treatment of pulmonary arterial hypertension in patients with NYHA class II-IV symptoms to diminish symptoms associated with exercise.

PRESENTATION – Vials (20 mg) for s.c. infusion containing treprostinil sodium equivalent to 1.0, 2.5, 5.0 and 10.0 mg/ml treprostinil.

PROPRIETARY NAME – Remodulin (US).

SOURCE – United Therapeutics.

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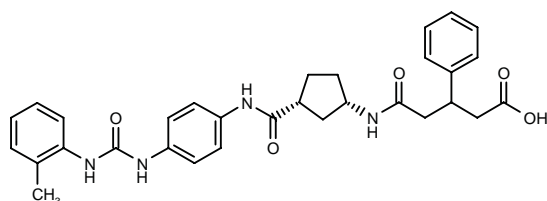
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TREATMENT OF DISORDERS OF THE CORONARY ARTERIES AND ATHEROSCLEROSIS

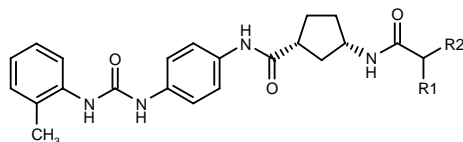
320461

N-[*(1S*,3R*)*-3-[*N*-[4-[3-(2-Methylphenyl)ureido]phenyl]carbamoyl]cyclopentyl]-3-phenylglutaramic acid



C31 H34 N4 O5; Mol wt: 542.6326

ACTION – Integrin ($\alpha_4\beta_1$, $\alpha_4\beta_7$ and/or $\alpha_9\beta_1$) antagonist shown to prevent cell adhesion to VCAM-1-coated plates with an IC_{50} of $< 10 \mu M$. Potentially useful for the treatment of atherosclerosis, asthma, chronic obstructive pulmonary disease, allergy, diabetes, inflammatory bowel disease, multiple sclerosis, myocardial ischemia, rheumatoid arthritis and transplant rejection, among other inflammatory, autoimmune and immune disorders. Other exemplified compounds are:



Compound	R1	R2	Formula
320462	CH ₂ CH ₂ CO ₂ H	(S)-NH ₂	C ₂₅ H ₃₁ N ₅ O ₅
320463	CH ₂ CH ₂ CO ₂ H	H	C ₂₅ H ₃₀ N ₄ O ₅
320464	(CH ₂) ₃ CO ₂ H	H	C ₂₆ H ₃₂ N ₄ O ₅
320465	CH ₂ CH(SPh)CO ₂ H	H	C ₃₁ H ₃₄ N ₄ O ₅ S
320466	(R)-CH(Me)CH ₂ CO ₂ H	H	C ₂₆ H ₃₂ N ₄ O ₅
320467	(R)-CH(OH)CH ₂ CO ₂ H	H	C ₂₅ H ₃₀ N ₄ O ₆
320468	(S)-CH(CO ₂ H)NHAc	H	C ₂₆ H ₃₁ N ₅ O ₆
320469	C(Me) ₂ CH ₂ CO ₂ H	H	C ₂₇ H ₃₄ N ₄ O ₅
320470	CH(4-Cl-Ph)CH ₂ CO ₂ H	H	C ₃₁ H ₃₃ ClN ₄ O ₅
320471	C(Me)(Ph)CH ₂ CO ₂ H	H	C ₃₂ H ₃₆ N ₄ O ₅

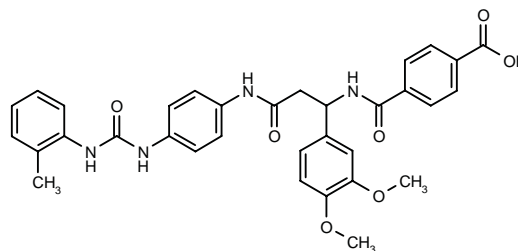
SOURCE – Bayer.

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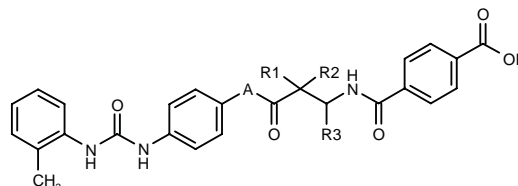
320477

4-[*N*-[1-(3,4-Dimethoxyphenyl)-2-[*N*-[4-[3-(2-methylphenyl)ureido]phenyl]carbamoyl]ethyl]carbamoyl]benzoic acid



C33 H32 N4 O7; Mol wt: 596.6368

ACTION – Integrin ($\alpha_4\beta_1$, $\alpha_4\beta_7$ and/or $\alpha_9\beta_1$) antagonist shown to prevent cell adhesion to VCAM-1-coated plates with an IC_{50} of $< 1 \mu M$. Potentially useful for the treatment of atherosclerosis, asthma, chronic obstructive pulmonary disease, allergy, diabetes, inflammatory bowel disease, multiple sclerosis, myocardial ischemia, rheumatoid arthritis and transplant rejection, among other inflammatory, autoimmune and immune disorders. Other exemplified β -amino acid derivatives are:



Compound	R1	R2	R3	A	Formula
320480		-(CH ₂) ₅ -	H	-CH ₂ NH-	C ₃₁ H ₃₄ N ₄ O ₅
320482	H	H	3,4-(MeO) ₂ -Ph	-CH ₂ NH-	C ₃₄ H ₃₄ N ₄ O ₇
320483	H	H	3-MeO-Ph	-NH-	C ₃₂ H ₃₀ N ₄ O ₆

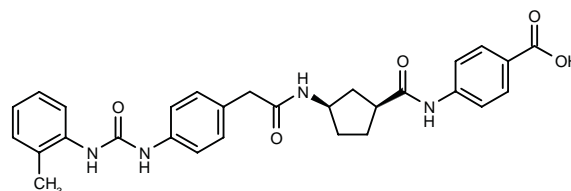
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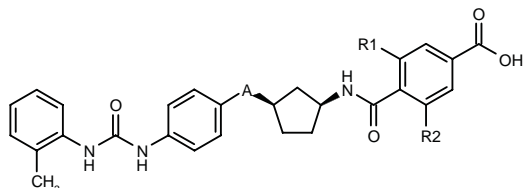
320508

4-[(1*S**,3*R**)-3-[2-[4-[3-(2-Methylphenyl)ureido]phenyl]-acetamido]cyclopentylcarboxamido]benzoic acid



C29 H30 N4 O5; Mol wt: 514.5790

ACTION – Integrin ($\alpha_4\beta_1$, $\alpha_4\beta_7$ and/or $\alpha_9\beta_1$) antagonist shown to prevent cell adhesion to VCAM-1-coated plates with an IC_{50} of $< 10 \mu M$. Potentially useful for the treatment of atherosclerosis, asthma, chronic obstructive pulmonary disease, allergy, diabetes, inflammatory bowel disease, multiple sclerosis, myocardial ischemia, rheumatoid arthritis and transplant rejection, among other inflammatory, autoimmune and immune disorders. Other exemplified cyclic carboxylic acids are:



Compound	R1=R2	A	Isomer	Formula
320509	H	-NHCO-	cis	$C_{28}H_{28}N_4O_5$
320510	H	-CH ₂ NHCO-	cis	$C_{29}H_{30}N_4O_5$
320511	Me	-CH ₂ NHCO-	cis	$C_{31}H_{34}N_4O_5$
320513	Me	-NHCO-	1S,3R	$C_{30}H_{32}N_4O_5$

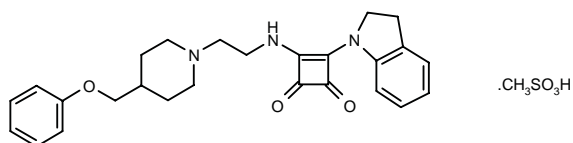
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320518

3-(2,3-Dihydro-1*H*-indol-1-yl)-4-[2-[4-(phenoxyethyl)-piperidin-1-yl]ethylamino]-3-cyclobutene-1,2-dione methanesulfonate



C₂₆ H₂₉ N₃ O₃ . C H₄ O₃ S; Mol wt: 527.6387

ACTION – A representative compound from a series of 3-cyclobutene-1,2-dione derivatives for use in the treatment of disorders associated with endothelial dysfunction including atherosclerosis, myocardial ischemia, heart failure, pulmonary hypertension and postoperative cardiovascular complications. The compound inhibited endothelial dysfunction induced by LNA in rat aortic preparations by 27% and that induced by xanthine oxidase-hypoxanthine in rabbit aortic rings by 17% at a concentration of $0.1 \mu M$. In rat aortic rings, compound also induced a 39% increase in acetylcholine-stimulated production of cGMP.

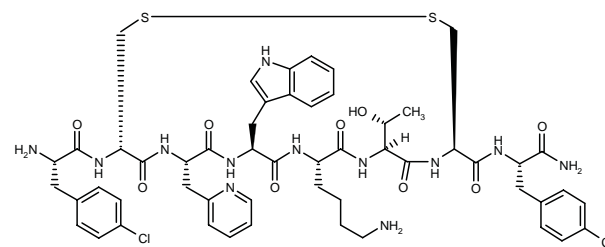
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320929

4-Chloro-L-phenylalanyl-D-cysteiny-3-(2-pyridyl)-L-alanyl-L-tryptophyl-L-lysyl-L-threonyl-L-cysteiny-4-chloro-L-phenylalaninamide cyclic disulfide



C₅₃ H₆₄ Cl₂ N₁₂ O₉ S₂; Mol wt: 1148.2020

ACTION – A representative compound from a series of cyclic peptides that act as modulators of urotensin-II receptors. Compound was able to inhibit urotensin-induced contractions in rat aortic rings with an IC_{50} of 2 nM, demonstrating its antagonist activity. Potentially useful for the treatment of ischemic heart disease, congestive heart failure, portal hypertension and variceal bleeding, as well as hypotension, angina pectoris, myocardial infarction, ulcer, anxiety, schizophrenia, manic depression, delirium, dementia, mental retardation and dyskinesia.

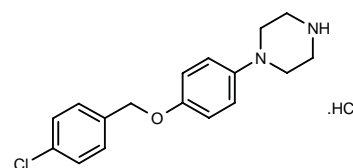
SOURCES – Biomeasure; Tulane Educational Fund, New Orleans, LA (US).

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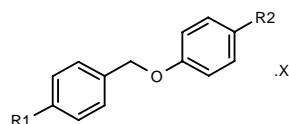
320930

1-[4-(4-Chlorobenzoyloxy)phenyl]piperazine hydrochloride



C₁₇ H₁₉ Cl N₂ O . HCl; Mol wt: 339.2640

ACTION – Na^+/Ca^{2+} exchange (NCX) inhibitor proven to inhibit Ca^{2+} uptake in NCX-1-transfected CCL-39 cells by 78.5% at $5 \mu M$. In a rat model of renal ischemia, i.p. administration of a dose of 10 mg/kg compound resulted in a 55.2% decrease in the plasma levels of urea nitrogen. Potentially useful for the treatment of myocardial infarction, cerebral infarction, ischemic nephropathy, hypertension, heart failure, arrhythmia, glaucoma, pigmentary retinal dystrophy, macular degeneration, ischemic optic neuropathy, iridocyclitis, occlusion of retinal artery and diabetic retinopathy. Other exemplified 4-benzoyloxyphenyl derivatives are:



Compound	R1	R2	X	Formula
320934	F	1-Piz	2HCl	C ₁₇ H ₁₉ FN ₂ O.2HCl
320935	F	1-Piz-CH ₂ CH ₂	2HCl	C ₁₉ H ₂₃ FN ₂ O.2HCl
320936	NO ₂	4-(CO ₂ Et)-2-thiazolidinyl-CH ₂		C ₂₀ H ₂₂ N ₂ O ₅ S

SOURCE – Senju.

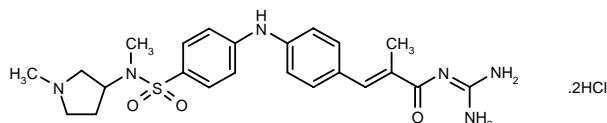
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ANTIARRHYTHMIC DRUGS

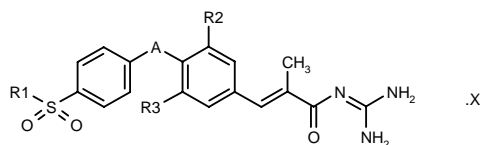
320090

N-(Diaminomethylene)-2-methyl-3-[4-[4-[*N*-methyl-*N*-(1-methylpyrrolidin-3-yl)sulfamoyl]phenylamino]phenyl]-2-propenamide dihydrochloride



C₂₃ H₃₀ N₆ O₃ S . 2HCl; Mol wt: 543.5168

ACTION – Na⁺/H⁺ exchanger subtype 3 (NHE3) inhibitor (IC₅₀ = 0.59 μM) with potential in the treatment of arrhythmia, as well as myocardial infarction, angina pectoris, ischemic disorders of the heart, peripheral and central nervous system and organs, and proliferative diseases, and for preserving organs for transplantation. Other exemplified guanidine derivatives are:



Compound	R1	R2	R3	A	X	Formula
320091	NHCH ₂ CH ₂ N(Me) ₂	F	F	O	2HCl	C ₂₁ H ₂₅ F ₂ N ₅ O ₄ S.2HCl
320092	4-Me-1-Piz	F	F	O	2CF ₃ CO ₂ H	C ₂₂ H ₂₅ F ₂ N ₅ O ₄ S. 2C ₂ HF ₃ O ₂
320093	NHCH ₂ CH ₂ N(Me) ₂	H	H	NH	2HCl	C ₂₁ H ₂₈ N ₆ O ₃ S.2HCl
320094	1-pyrrolidinyl-CH ₂ CH ₂ NH	H	H	NH	2HCl	C ₂₃ H ₃₀ N ₆ O ₃ S.2HCl
320095	4-Me-1-Piz	H	H	NH	2HCl	C ₂₂ H ₂₈ N ₆ O ₃ S.2HCl

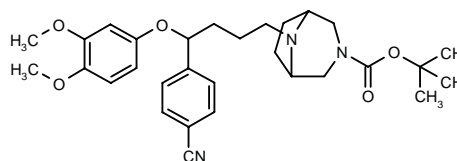
SOURCE – Aventis Pharma.

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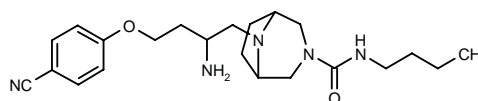
320582

8-[4-(4-Cyanophenyl)-4-(3,4-dimethoxyphenoxy)butyl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylic acid *tert*-butyl ester



C₃₀ H₃₉ N₃ O₅; Mol wt: 521.6541

ACTION – Antiarrhythmic agent, particularly useful for the treatment of atrial and ventricular arrhythmias. Another exemplified 3,8-diazabicyclo[3.2.1]octane is:



320583: C₂₂ H₃₃ N₅ O₂

SOURCE – AstraZeneca.

REFERENCES

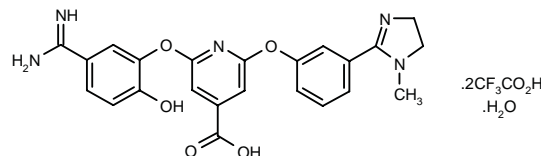
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AGENTS AFFECTING BLOOD COAGULATION

ANTICOAGULANTS

319412

2-(5-Amidino-2-hydroxyphenoxy)-6-[3-(1-methyl-4,5-dihydro-1H-imidazol-2-yl)phenoxy]pyridine-4-carboxylic acid bis(trifluoroacetate) monohydrate



C₂₃ H₂₁ N₅ O₅ . 2 C₂ H₃ F₃ O₂ . H₂O; Mol wt: 693.5075

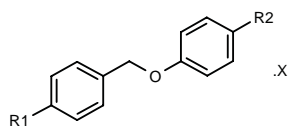
ACTION – Anticoagulant, a potent, and selective factor Xa inhibitor with IC₅₀ values of 2.4, 810 and 220 nM against factor Xa, factor IIa and trypsin, respectively.

SOURCE – Berlex.

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Compound	R1	R2	X	Formula
320934	F	1-Piz	2HCl	C ₁₇ H ₁₉ FN ₂ O ₂ ·2HCl
320935	F	1-Piz-CH ₂ CH ₂	2HCl	C ₁₉ H ₂₃ FN ₂ O ₂ ·2HCl
320936	NO ₂	4-(CO ₂ Et)-2-thiazolidinyl-CH ₂		C ₂₀ H ₂₂ N ₂ O ₅ S

SOURCE – Senju.

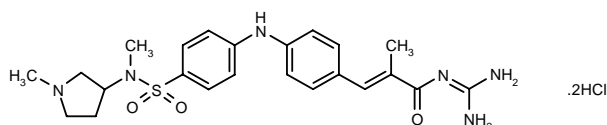
REFERENCES

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ANTIARRHYTHMIC DRUGS

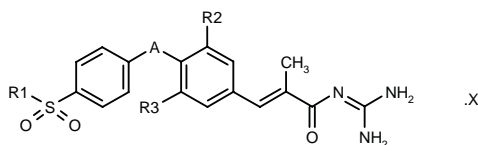
320090

N-(Diaminomethylene)-2-methyl-3-[4-[4-[*N*-methyl-*N*-(1-methylpyrrolidin-3-yl)sulfamoyl]phenylamino]phenyl]-2-propenamide dihydrochloride



C₂₃ H₃₀ N₆ O₃ S . 2HCl; Mol wt: 543.5168

ACTION – Na⁺/H⁺ exchanger subtype 3 (NHE3) inhibitor (IC₅₀ = 0.59 μM) with potential in the treatment of arrhythmia, as well as myocardial infarction, angina pectoris, ischemic disorders of the heart, peripheral and central nervous system and organs, and proliferative diseases, and for preserving organs for transplantation. Other exemplified guanidine derivatives are:



Compound	R1	R2	R3	A	X	Formula
320091	NHCH ₂ CH ₂ N(Me) ₂	F	F	O	2HCl	C ₂₁ H ₂₅ F ₂ N ₅ O ₄ S·2HCl
320092	4-Me-1-Piz	F	F	O	2CF ₃ CO ₂ H	C ₂₂ H ₂₅ F ₂ N ₅ O ₄ S·2C ₂ H ₃ FO ₂
320093	NHCH ₂ CH ₂ N(Me) ₂	H	H	NH	2HCl	C ₂₁ H ₂₈ N ₆ O ₃ S·2HCl
320094	1-pyrrolidinyl-CH ₂ CH ₂ NH	H	H	NH	2HCl	C ₂₃ H ₃₀ N ₆ O ₃ S·2HCl
320095	4-Me-1-Piz	H	H	NH	2HCl	C ₂₂ H ₂₈ N ₆ O ₃ S·2HCl

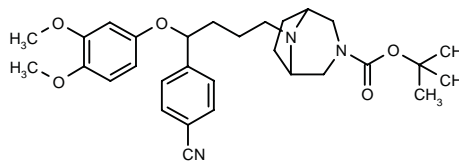
SOURCE – Aventis Pharma.

REFERENCES

1. Hofmeister, A. et al. (Aventis Pharma Deutschland GmbH) *Subst. cinnamic acid guanidides, method for the production thereof, their use as a medicament, and to a medicament containing these cpds.* DE 10046993, US 2002058710, WO 0224637.

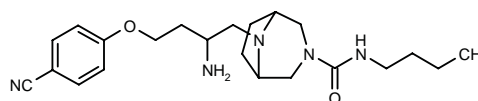
320582

8-[4-(4-Cyanophenyl)-4-(3,4-dimethoxyphenoxy)butyl]-3,8-diazabicyclo[3.2.1]octane-3-carboxylic acid *tert*-butyl ester



C₃₀ H₃₉ N₃ O₅; Mol wt: 521.6541

ACTION – Antiarrhythmic agent, particularly useful for the treatment of atrial and ventricular arrhythmias. Another exemplified 3,8-diazabicyclo[3.2.1]octane is:



320583: C₂₂ H₃₃ N₅ O₂

SOURCE – AstraZeneca.

REFERENCES

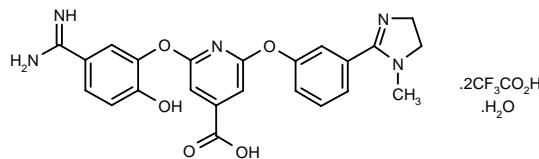
1. Björnsne, M. et al. (AstraZeneca AB) *3,8-Diazabicyclo[3.2.1]octanes and their use in the treatment of cardiac arrhythmias*. WO 0232902.

AGENTS AFFECTING BLOOD COAGULATION

ANTICOAGULANTS

319412

2-(5-Amidino-2-hydroxyphenoxy)-6-[3-(1-methyl-4,5-dihydro-1*H*-imidazol-2-yl)phenoxy]pyridine-4-carboxylic acid bis(trifluoroacetate) monohydrate



C₂₃ H₂₁ N₅ O₅ . 2 C₂ H F₃ O₂ . H₂O; Mol wt: 693.5075

ACTION – Anticoagulant, a potent, and selective factor Xa inhibitor with IC₅₀ values of 2.4, 810 and 220 nM against factor Xa, factor IIa and trypsin, respectively.

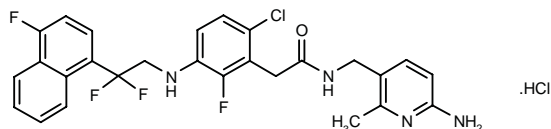
SOURCE – Berlex.

REFERENCES

- Phillips, G. et al. *Design, synthesis, and activity of a novel series of factor Xa inhibitors: Optimization of arylamidino groups*. J Med Chem 2002, 45(12): 2484.
- Phillips, G.B. et al. *Discovery of N-[2-[5-amino(imino)methyl]-2-hydroxyphenoxy]-3,5-difluoro-6-[3-(4,5-dihydro-1-methyl-1*H*-imidazol-2-yl)phenoxy]pyridin-4-yl]-*N*-methylglycine (ZK-807834): A potent, selective, and orally active inhibitor of the blood coagulation enzyme factor Xa*. J Med Chem 1998, 41(19): 3557.

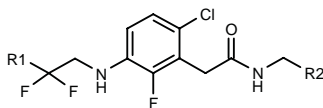
319705

N-(6-Amino-2-methylpyridin-3-ylmethyl)-2-[6-chloro-3-[2,2-difluoro-2-(4-fluoronaphthalen-1-yl)ethylamino]-2-fluorophenyl]acetamide hydrochloride

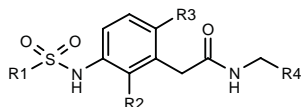


C27 H23 Cl F4 N4 O . HCl; Mol wt: 567.4116

ACTION – An inhibitor of trypsin-like proteases, especially thrombin ($K_i = 0.0028 \mu\text{M}$). Potentially useful for the treatment of thrombotic disorders including ischemic stroke, restenosis, inflammation and venous and arterial thrombosis. Other specifically claimed compounds are:



Compound	R1	R2	Formula
319709	Ph	CH2ONHC(=NH)NH2	C ₁₉ H ₂₁ ClF ₃ N ₅ O ₂
319711	Ph	6-NH2-2-Me-3-Pyr	C ₂₃ H ₂₂ ClF ₃ N ₄ O
319712	4-F-1-Naph	CH2ONHC(=NH)NH2	C ₂₃ H ₂₂ ClF ₄ N ₅ O ₂



Compound	R1	R2	R3	R4	Formula
319713	CH2Ph	H	H	CH2ONHC(=NH)NH2	C ₁₈ H ₂₃ N ₅ O ₄ S
319714	CH2Ph	H	Cl	CH2ONHC(=NH)NH2	C ₁₈ H ₂₂ ClN ₅ O ₄ S
319715	CH2Ph	H	Me	CH2ONHC(=NH)NH2	C ₁₉ H ₂₅ N ₅ O ₄ S
319716	3-Me-Ph	OH	Me	CH2ONHC(=NH)NH2	C ₁₉ H ₂₅ N ₅ O ₅ S
319717	3-Me-Ph	OH	Me	6-NH2-2-Me-3-Pyr	C ₂₃ H ₂₆ N ₄ O ₄ S

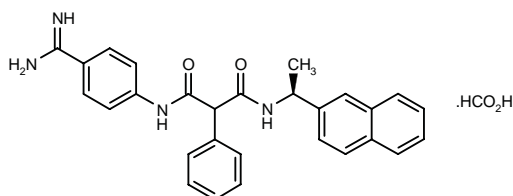
SOURCE – 3-Dimensional Pharmaceuticals.

REFERENCES

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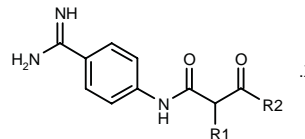
319723

*N*¹-(4-Amidinophenyl)-*N*³-[1(*S*)-(2-naphthyl)ethyl]-2-phenylmalonamide formate



C28 H26 N4 O2 . C H2 O2; Mol wt: 496.5642

ACTION – Anticoagulant that acts as an inhibitor of factor VIIa ($K_i = 0.124 \mu\text{M}$). Potentially useful for the treatment of thromboembolic diseases and restenosis. Other exemplified compounds within this series of malonamide and malonamic acid ester derivatives are:



Compound	R1	R2	X	Formula
319724	Ph	OCH2Ph		C ₂₃ H ₂₁ N ₃ O ₃
319727	Ph	4-NO2-PhCH(Me)NH	HCO2H	C ₂₄ H ₂₃ N ₅ O ₄ .CH ₂ O ₂
319728	Ph	NHCH(CN)Ph	HCO2H	C ₂₄ H ₂₁ N ₅ O ₂ .CH ₂ O ₂
319730	Ph	(S)-7-MeO-1,2,3,4-tetrahydro-2-Naph-NH	HCO2H	C ₂₇ H ₂₈ N ₄ O ₃ .CH ₂ O ₂
319731	Ph	(S)-4-Br-PhCH(Me)NH	HCO2H	C ₂₄ H ₂₃ BrN ₄ O ₂ .CH ₂ O ₂
319732	Ph	2-(OPh)-6-Cl-PhCH2NH	HCO2H	C ₂₉ H ₂₅ ClN ₄ O ₃ .CH ₂ O ₂
319733	Ph	4-Ph-PhCH2NH	HCO2H	C ₂₈ H ₂₆ N ₄ O ₂ .CH ₂ O ₂
319734	Ph	(4-MeO-Ph)2CHNH	HCO2H	C ₃₁ H ₃₀ N ₄ O ₄ .CH ₂ O ₂
319735	Ph	(S)-4-MeO-PhCH(Me)NH	HCO2H	C ₂₈ H ₂₆ N ₄ O ₃ .CH ₂ O ₂
319736	Ph	4-(1,2,3-thiadiazol-4-yl)-PhCH2NH	HCO2H	C ₂₅ H ₂₂ N ₆ O ₂ S .CH ₂ O ₂
319737	Ph	3-NO2-PhCH2NH	HCO2H	C ₂₃ H ₂₁ N ₅ O ₄ .CH ₂ O ₂
319738	Ph	3,4-(MeO)2-PhCH2NH		C ₂₅ H ₂₆ N ₄ O ₄
319739	CH2CH2Ph	NHCH2Ph		C ₂₅ H ₂₆ N ₄ O ₂
319741	CH2CH2Ph	(S)-2-Naph-CH(Me)NH		C ₃₀ H ₃₀ N ₄ O ₂
319743	H	(S)-2-Naph-CH(Me)NH	CF3CO2H	C ₂₂ H ₂₂ N ₄ O ₂ .C ₂ HF ₃ O ₂

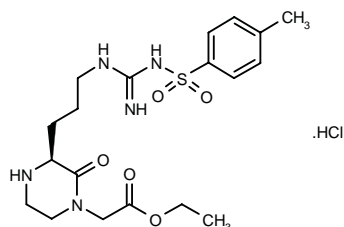
SOURCE – Aventis Pharma.

REFERENCES

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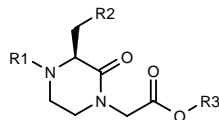
320216

2-[3(*S*)-[3-[*N*²-(4-Methylphenylsulfonyl)guanidino]propyl]-2-oxopiperazin-1-yl]acetic acid ethyl ester hydrochloride

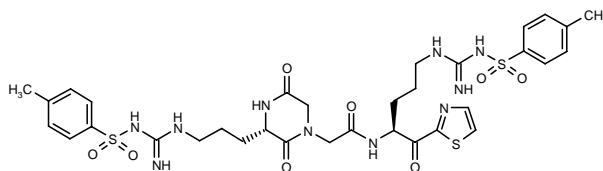


C19 H29 N5 O5 S . HCl ; Mol wt: 475.9950

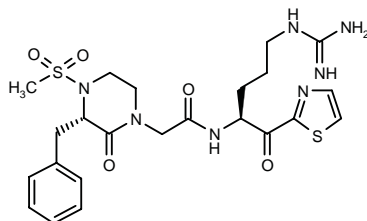
ACTION – Agent with the ability to inhibit factor Xa, potentially useful for the treatment of undesired thrombosis associated with unstable and refractory angina, myocardial infarction, transient ischemic attacks, stroke, disseminated intravascular coagulation, septic shock, deep venous thrombosis, pulmonary embolism and reocclusion or restenosis of reperfused coronary arteries. Other exemplified compounds include the following:



Compound	R1	R2	R3	Formula
320217	H	4-MePhSO ₂ NHC(=NH)NHCH ₂ CH ₂	H	C ₁₇ H ₂₅ N ₅ O ₅ S
320219	H	Ph	Et	C ₁₅ H ₂₀ N ₂ O ₃
320220	t-BuOCO	Ph	Et	C ₂₀ H ₂₈ N ₂ O ₅



320218: C₃₃ H₄₂ N₁₀ O₈ S₃



320217: C₁₇ H₂₅ N₅ O₅ S

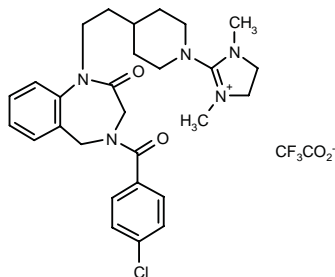
SOURCE – Millennium.

REFERENCES

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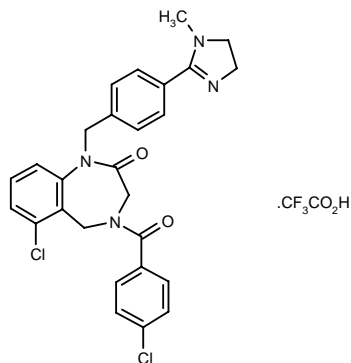
320255

2-[4-[2-[4-(4-Chlorobenzoyl)-2-oxo-2,3,4,5-tetrahydro-1H-1,4-benzodiazepin-1-yl]ethyl]piperidin-1-yl]-1,3-dimethyl-4,5-dihydro-1H-imidazol-3-ium trifluoroacetate

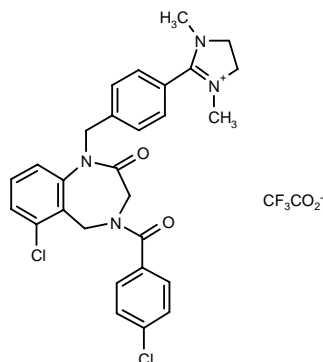


C₃₀ H₃₅ Cl F₃ N₅ O₄ ; Mol wt: 622.0845

ACTION – Factor Xa inhibitor (pIC₅₀ = 7.1) shown to be selective with respect to thrombin. Potentially useful as an anticoagulant for the treatment of cerebral infarction, cerebral thrombosis, acute and chronic myocardial infarction, unstable angina, peripheral arterial obstruction, deep venous thrombosis, intravascular coagulation syndrome, postangioplasty reocclusion and restenosis, etc. Other exemplified benzodiazepine derivatives are:



320256: C₂₇ H₂₄ Cl₂ N₄ O₂ . C₂ H F₃ O₂



320258: C₃₀ H₂₇ Cl₂ F₃ N₄ O₄

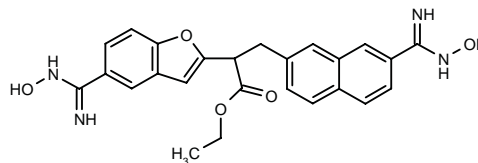
SOURCE – Ajinomoto.

REFERENCES

1. Nakagawa, T. et al. (Ajinomoto Co., Inc.) *Benzodiazepine deriv.* WO 0226732.

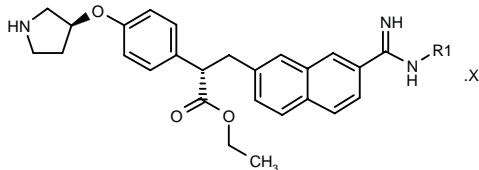
320342

2-[5-(N-Hydroxyamidino)-1-benzofuran-2-yl]-3-[7-(N-hydroxyamidino)naphthalen-2-yl]propionic acid ethyl ester

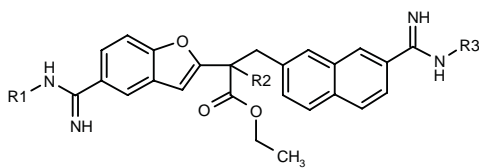


C₂₅ H₂₄ N₄ O₅; Mol wt: 460.4876

ACTION – Factor Xa inhibitor that demonstrated *in vivo* activity following oral administration to rats at a dose of 44.4. mg/kg, with factor Xa-inhibitory rates of 68.7, 64.4 and 17.1%, respectively, measured 1, 4 and 24 h after dosing. Potentially useful for the treatment of thrombo-embolic disorders associated with angina pectoris, cerebral infarction, cerebral embolism, myocardial infarction, pulmonary infarction, pulmonary embolism, deep venous thrombosis, disseminated intravascular coagulation, intermittent claudication, etc. Other exemplified compounds are:



Compound	R1	X	Formula
320344	OH	CF ₃ CO ₂ H	C ₂₆ H ₂₉ N ₃ O ₄ ·C ₂ HF ₃ O ₂
320350	CO ₂ Me	HCl	C ₂₈ H ₃₁ N ₃ O ₅ ·HCl



Compound	R1	R2	R3	Formula
320348	OH	CO ₂ Et	OH	C ₂₈ H ₂₈ N ₄ O ₇
320351	CO ₂ Me	H	CO ₂ Me	C ₂₉ H ₂₈ N ₄ O ₇

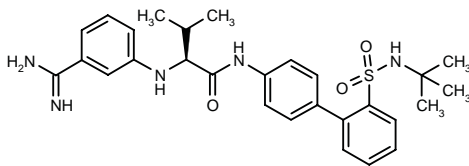
SOURCE – Daiichi Pharmaceutical.

REFERENCES

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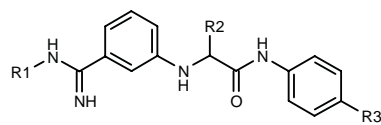
320537

*N*²-(3-Amidinophenyl)-*N*¹-[2'-(*N*-*tert*-butylsulfamoyl)-biphenyl-4-yl]-L-valinamide



C₂₈ H₃₅ N₅ O₃ S; Mol wt: 521.6825

ACTION – Factor Xa inhibitor with potential as an anticoagulant in the treatment of thrombosis, myocardial infarction, arteriosclerosis, inflammation, stroke, angina pectoris, postangioplasty restenosis and intermittent claudication. Other specifically claimed *N*-substituted amino acids include the following:



Compound	R1	R2	R3	Isomer	Formula
320538	H	(CH ₂) ₄ NH ₂	2-(NH ₂ SO ₂)-Ph	S	C ₂₅ H ₃₀ N ₆ O ₃ S
320539	H	CH ₂ CO ₂ H	2-(NH ₂ SO ₂)-Ph	S	C ₂₃ H ₂₃ N ₅ O ₅ S
320540	H	i-Pr	2-(t-BuNH ₂ SO ₂)-Ph	R	C ₂₈ H ₃₅ N ₅ O ₃ S
320541	OH	i-Pr	2-(NH ₂ SO ₂)-Ph	S	C ₂₄ H ₂₇ N ₅ O ₄ S
320542	OH	Me	2-(NH ₂ SO ₂)-Ph		C ₂₂ H ₂₃ N ₅ O ₄ S
320543	H	CH ₂ CO ₂ H	2-(MeSO ₂)-Ph	S	C ₂₄ H ₂₄ N ₄ O ₅ S
320544	H	CH(Me)Et	2-(MeSO ₂)-Ph	S	C ₂₆ H ₃₀ N ₄ O ₅ S
320545	H	CH ₂ OMe	4-Pyr	S	C ₂₂ H ₂₃ N ₅ O ₂

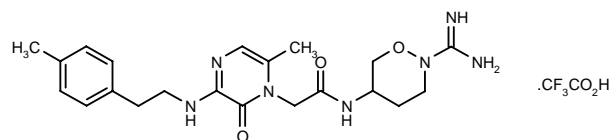
SOURCE – Merck KGaA.

REFERENCES

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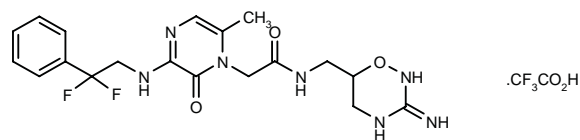
320927

N-(2-Amidinoperhydro-1,2-oxazin-5-yl)-2-[6-methyl-3-[2-(4-methylphenyl)ethylamino]-2-oxo-1,2-dihydropyrazin-1-yl]acetamide trifluoroacetate



C₂₁ H₂₉ N₇ O₃ . C₂ H₃ F₃ O₂; Mol wt: 541.5280

ACTION – Potent and selective thrombin inhibitor (*K_i* = 0.6-1.3 nM), potentially useful as an antithrombotic agent. Another exemplified cyclic oxyguanidine pyrazinone is:



320928: C₁₉ H₂₃ F₂ N₇ O₃ . C₂ H₃ F₃ O₂

SOURCE – 3-Dimensional Pharmaceuticals.

REFERENCES

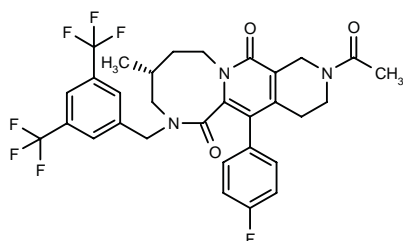
1. Wang, A. et al. (3-Dimensional Pharmaceuticals, Inc.) *Cyclic oxyguanidine pyrazinones as protease inhibitors*. US 2002052357.

RENAL-UROLOGIC DRUGS

TREATMENT OF URINARY INCONTINENCE

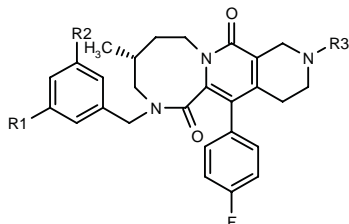
319962

10-Acetyl-2-[3,5-bis(trifluoromethyl)benzyl]-13-(4-fluorophenyl)-4(*R*)-methyl-2,3,4,5,6,8,9,10,11,12-decahydro-1*H*-[1,4]diazocino[1,2-*b*]-2,7-naphthyridine-1,8-dione

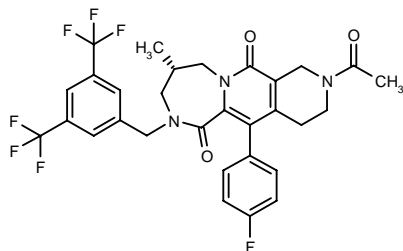


C31 H28 F7 N3 O3; Mol wt: 623.5662

ACTION – Tachykinin antagonist, potentially useful for the treatment of pollakiuria and urinary incontinence, CNS disorders such as depression, anxiety, manic depressive psychosis and schizophrenia, and also other tachykinin-mediated disorders including inflammatory and allergic conditions, pain, migraine, neuralgia, itching, cough, HIV infection, chronic obstructive pulmonary disease, digestive diseases, vomiting, cardiovascular diseases and immune disorders. Other exemplified tricyclic heterocyclic compounds are:



Compound	R1	R2	R3	Formula
319964	CF3	CF3	COEt	C ₃₂ H ₃₀ F ₇ N ₃ O ₃
319965	Me	Me	Me	C ₃₀ H ₃₄ FN ₃ O ₂



319963: C30 H26 F7 N3 O3

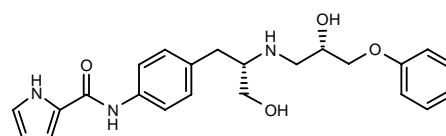
SOURCE – Takeda.

REFERENCES

1. Ikeura, Y. et al. (Takeda Chemical Industries, Ltd.) *Tricyclic heterocyclic cpds., process for producing the same, and use thereof*. JP 2002155084, WO 0222574.

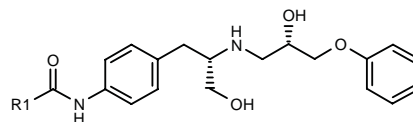
320080

N-[4-[3-Hydroxy-2(*S*)-[2(*S*)-hydroxy-3-phenoxypropyl-amino]propyl]phenyl]-1*H*-pyrrole-2-carboxamide



C23 H27 N3 O4; Mol wt: 409.4833

ACTION – β_3 -Adrenoceptor agonist for use in the treatment of pollakiuria, urinary incontinence, obesity and diabetes. Intraduodenal administration of compound to anesthetized dogs at a dose of 0.32 mg/kg resulted in 63% inhibition of the carbachol-induced increase in intravesicular pressure. Other specifically claimed amino-alcohol derivatives are:



Compound	R1	Formula
320081	NHPh	C ₂₅ H ₂₉ N ₃ O ₄
320082	1-Naph	C ₂₉ H ₃₀ N ₂ O ₄
320083	3-F-PhNH	C ₂₅ H ₂₈ FN ₃ O ₄
320084	3-MeO-PhNH	C ₂₆ H ₃₁ N ₃ O ₅

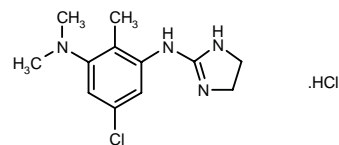
SOURCE – Fujisawa.

REFERENCES

1. Sakurai, M. et al. (Fujisawa Pharmaceutical Co., Ltd.) *Aminoalcohol derivs*. WO 0224635.

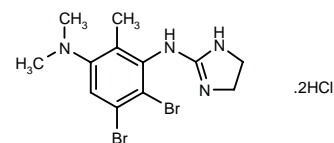
320506

5-Chloro-*N*¹-(4,5-dihydro-1*H*-imidazol-2-yl)-*N*³,*N*³,2-trimethylbenzene-1,3-diamine hydrochloride



C12 H17 Cl N4 . HCl; Mol wt: 289.2082

ACTION – Agent for the treatment of urinary incontinence, reported to have an oral bioavailability of 11% in rats and to exert *in vivo* activity in dogs. Another exemplified imidazolidine derivative is:



320507: C12 H16 Br2 N4 . 2HCl

SOURCE – Boehringer Ingelheim.

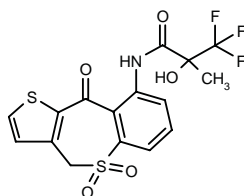
REFERENCES

- Esser, F. et al. (Boehringer Ingelheim Pharma KG) *Novel m-amino-phenylimino-imidazolidine derivs. for treating urinary incontinence*. WO 0232876.

KW-7158*

270489

3,3,3-Trifluoro-2-hydroxy-2-methyl-*N*-(10-oxo-4,10-dihydrothieno[3,2-*c*][1]benzothiepin-9-yl)propanamide 5,5-dioxide



C₁₆ H₁₂ F₃ N O₅ S₂; Mol wt: 419.3988

ACTION – Putative bladder afferent nerve inhibitor proven to depress detrusor hyperactivity in the bladder. In normal rats, compound (10 and 100 µg/kg i.v.) increased the bladder intercontraction interval without modifying large-amplitude reflex bladder contractions or the volume threshold. In the rat model of xylene-induced bladder irritation, the above doses ameliorated the volume threshold and the intercontraction interval, induced small-amplitude unstable bladder contractions and suppressed arterial pressor responses induced during large-amplitude bladder contractions or by bladder distension. Currently undergoing phase II clinical evaluation for the treatment of urinary urgency, frequent urination and urinary incontinence associated with bladder overactivity.

SOURCE – Kyowa Hakko.

REFERENCES

- Imai, E. et al. (Kyowa Hakko Kogyo Co., Ltd.) *Preparation method of tricyclic cpds*. JP 2002053580.
- Yoshida, M. et al. (Kyowa Hakko Kogyo Co., Ltd.) *Tricyclic cpds*. EP 0979821, US 6211227, WO 9846587.
- Lu, S.-H. et al. *Effect of KW-7158, a novel putative afferent nerve inhibitor, on bladder and vesico-vascular reflexes in rats with normal and irritated bladders*. J Urol 2002, 167(4, Suppl.): Abst 973.
- Lu, S.-H. *Effects of KW-7158, a putative C-fiber afferent inhibitor, on detrusor activity and vesicovascular reflex in normal and irritated bladders of rats*. Soc Neurosci Abst 2001, 27: Abst 817.9.
- KW-7158 to enter phase II trials in Europe for treatment of urinary incontinence*. DailyDrugNews.com (Daily Essentials) 2001, June 8.
- Kyowa Hakko initiates phase I testing of treatment for urinary incontinence*. DailyDrugNews.com (Daily Essentials) 2000, July 3.
- Phase II trials begin in Europe and U.S. for KW-7158*. DailyDrugNews.com (Daily Essentials) 2002, May 16.

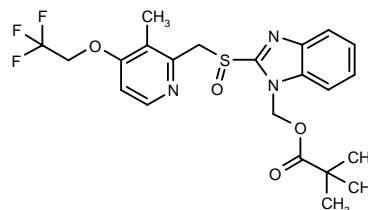
*Identified compound **270489** (see **270488**) Drug Data Rep 1999, 021(01): 0044.

GASTROINTESTINAL DRUGS

ANTIULCER DRUGS

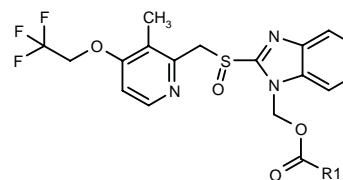
320792

2,2-Dimethylpropionic acid 2-[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-ylmethylsulfinyl]-1*H*-benzimidazol-1-ylmethyl ester



C₂₂ H₂₄ F₃ N₃ O₄ S; Mol wt: 483.5086

ACTION – An acid-stable prodrug of the proton pump inhibitor lansoprazole⁺, stable in artificial gastric solution (half-life = 13.8 h) and efficiently converted to the active compound in rat and human liver and small intestine preparations. Potentially useful for the treatment of gastrointestinal disorders such as ulcer, gastritis, reflux esophagitis, gastric cancer, gastric hyperacidity and hemorrhage of the upper digestive tract. Other exemplified benzimidazole compounds are:



Compound	R1	Formula
320794	Ph	C ₂₄ H ₂₀ F ₃ N ₃ O ₄ S
320795	OPr	C ₂₁ H ₂₂ F ₃ N ₃ O ₅ S

SOURCE – Takeda.

REFERENCES

- Kamiyama, K. and Sato, F. (Takeda Chemical Industries, Ltd.) *Benzimidazole cpds., process for producing the same and use thereof*. WO 0230920.

*Drug Data Rep 1992, 014(04): 0332.

SOURCE – Boehringer Ingelheim.

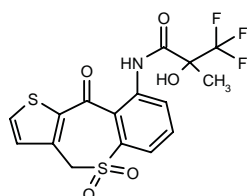
REFERENCES

- Esser, F. et al. (Boehringer Ingelheim Pharma KG) *Novel m-amino-phenylimino-imidazolidine derivs. for treating urinary incontinence*. WO 0232876.

KW-7158*

270489

3,3,3-Trifluoro-2-hydroxy-2-methyl-N-(10-oxo-4,10-dihydrothieno[3,2-c][1]benzothiepin-9-yl)propanamide 5,5-dioxide



C16 H12 F3 N O5 S2; Mol wt: 419.3988

ACTION – Putative bladder afferent nerve inhibitor proven to depress detrusor hyperactivity in the bladder. In normal rats, compound (10 and 100 µg/kg i.v.) increased the bladder intercontraction interval without modifying large-amplitude reflex bladder contractions or the volume threshold. In the rat model of xylene-induced bladder irritation, the above doses ameliorated the volume threshold and the intercontraction interval, induced small-amplitude unstable bladder contractions and suppressed arterial pressor responses induced during large-amplitude bladder contractions or by bladder distension. Currently undergoing phase II clinical evaluation for the treatment of urinary urgency, frequent urination and urinary incontinence associated with bladder overactivity.

SOURCE – Kyowa Hakko.

REFERENCES

- Imai, E. et al. (Kyowa Hakko Kogyo Co., Ltd.) *Preparation method of tricyclic cpds*. JP 2002053580.
- Yoshida, M. et al. (Kyowa Hakko Kogyo Co., Ltd.) *Tricyclic cpds*. EP 0979821, US 6211227, WO 9846587.
- Lu, S.-H. et al. *Effect of KW-7158, a novel putative afferent nerve inhibitor, on bladder and vesico-vascular reflexes in rats with normal and irritated bladders*. J Urol 2002, 167(4, Suppl.): Abst 973.
- Lu, S.-H. *Effects of KW-7158, a putative C-fiber afferent inhibitor, on detrusor activity and vesicovascular reflex in normal and irritated bladders of rats*. Soc Neurosci Abst 2001, 27: Abst 817.9.
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- Phase II trials begin in Europe and U.S. for KW-7158*. DailyDrugNews.com (Daily Essentials) 2002, May 16.

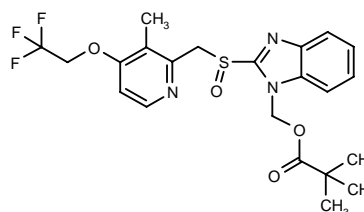
*Identified compound **270489** (see **270488**) Drug Data Rep 1999, 021(01): 0044.

GASTROINTESTINAL DRUGS

ANTIULCER DRUGS

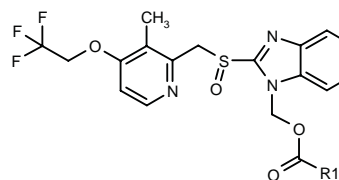
320792

2,2-Dimethylpropionic acid 2-[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-ylmethylsulfinyl]-1H-benzimidazol-1-ylmethyl ester



C22 H24 F3 N3 O4 S; Mol wt: 483.5086

ACTION – An acid-stable prodrug of the proton pump inhibitor lansoprazole⁺, stable in artificial gastric solution (half-life = 13.8 h) and efficiently converted to the active compound in rat and human liver and small intestine preparations. Potentially useful for the treatment of gastrointestinal disorders such as ulcer, gastritis, reflux esophagitis, gastric cancer, gastric hyperacidity and hemorrhage of the upper digestive tract. Other exemplified benzimidazole compounds are:



Compound	R1	Formula
320794	Ph	C ₂₄ H ₂₀ F ₃ N ₃ O ₄ S
320795	OPr	C ₂₁ H ₂₂ F ₃ N ₃ O ₅ S

SOURCE – Takeda.

REFERENCES

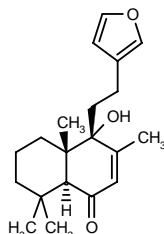
- Kamiyama, K. and Sato, F. (Takeda Chemical Industries, Ltd.) *Benzimidazole cpds., process for producing the same and use thereof*. WO 0230920.

*Drug Data Rep 1992, 014(04): 0332.

SOLIDAGENONE

320805

(4*R*,4*aS*,8*aS*)-4-[2-(3-Furyl)ethyl]-4-hydroxy-3,4*a*,8,8-tetramethyl-4*a*,5,6,7,8,8*a*-hexahydronaphthalen-1(4*H*)-one



C20 H28 O3; Mol wt: 316.4382

ACTION – Antiulcer agent, a labdane diterpene isolated from the rhizomes of *Solidago chilensis*, a plant used in traditional medicine for the treatment of inflammatory conditions. Compound exhibited gastroprotective activity (comparable to ranitidine 50 mg/kg) in rat models of gastric ulcers including pylorus ligation (37-47% reduction in ulcer index at 50-200 mg/kg p.o.), aspirin-induced ulcers (50% reduction at 100-200 mg/kg p.o.) and ethanol-induced gastric ulcers, where doses of 100 and 200 mg/kg produced an effect comparable to omeprazole 20 mg/kg. In mice, compound exhibit no toxicity at doses up to 600 mg/kg i.p.

SOURCE – Universidad de Talca, Talca (CL).

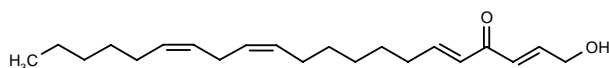
REFERENCES

1. Rodriguez, J.A. et al. *Gastroprotective activity of solidagenone on experimentally-induced gastric lesions in rats*. J Pharm Pharmacol 2002, 54(3): 399.

TREATMENT OF LIVER AND BILIARY TRACT DISORDERS

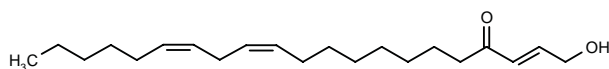
320328

1-Hydroxyhenicosa-2(*E*),5(*E*),12(*Z*),15(*Z*)-tetraen-4-one

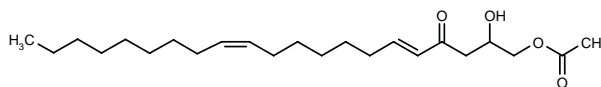


C21 H34 O2; Mol wt: 318.4976

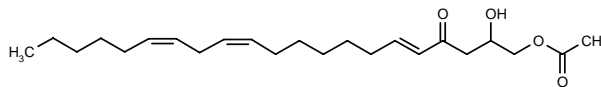
ACTION – Hepatoprotectant that may be obtained by chemical synthesis or isolated from a plant belonging to the avocado family. It demonstrated *in vivo* efficacy in a rat model of chronic hepatitis induced by D-galactosamine following intraduodenal administration at a dose of 100 mg/kg. Other exemplified compounds are:



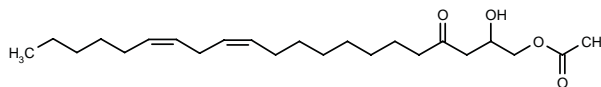
320329: C21 H36 O2



320330: C23 H40 O4



320331: C23 H38 O4



320332: C23 H40 O4

SOURCE – Kagome.

REFERENCES

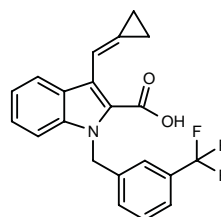
1. Arimoto, Y. et al. (Kagome Co., Ltd.) *Novel hepatopathy inhibitors*. JP 2002105017.

ENDOCRINE DRUGS

ANTIDIABETIC DRUGS

320593

3-(Cyclopropylidenemethyl)-1-[3-(trifluoromethyl)benzyl]-1*H*-indole-2-carboxylic acid



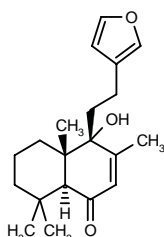
C21 H16 F3 N O2; Mol wt: 371.3564

ACTION – Peroxisome proliferator-activated receptor PPAR γ modulator, proven to inhibit the binding of [3 H]-BRL-49653 to PPAR γ receptors with an IC₅₀ of < 10 nM. Potentially useful for the treatment of osteopenia, cancer, hyperglycemia, diabetes, syndrome X, insulin resistance, dyslipidemia, hypertriglyceridemia, hypercholesterolemia and hyperlipidemia, inflammation, atherosclerosis, inflammatory bowel disease, Alzheimer's disease, rheumatoid arthritis, hypertension, obesity, skin disorders and lupus erythematosus. Other specifically claimed substituted indoles are:

SOLIDAGENONE

320805

(4*R*,4*aS*,8*aS*)-4-[2-(3-Furyl)ethyl]-4-hydroxy-3,4*a*,8,8-tetramethyl-4*a*,5,6,7,8,8*a*-hexahydronaphthalen-1(4*H*)-one



C20 H28 O3; Mol wt: 316.4382

ACTION – Antiulcer agent, a labdane diterpene isolated from the rhizomes of *Solidago chilensis*, a plant used in traditional medicine for the treatment of inflammatory conditions. Compound exhibited gastroprotective activity (comparable to ranitidine 50 mg/kg) in rat models of gastric ulcers including pylorus ligation (37-47% reduction in ulcer index at 50-200 mg/kg p.o.), aspirin-induced ulcers (50% reduction at 100-200 mg/kg p.o.) and ethanol-induced gastric ulcers, where doses of 100 and 200 mg/kg produced an effect comparable to omeprazole 20 mg/kg. In mice, compound exhibit no toxicity at doses up to 600 mg/kg i.p.

SOURCE – Universidad de Talca, Talca (CL).

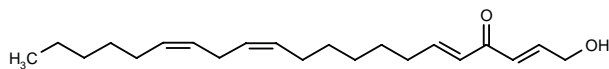
REFERENCES

1. Rodriguez, J.A. et al. *Gastroprotective activity of solidagenone on experimentally-induced gastric lesions in rats*. J Pharm Pharmacol 2002, 54(3): 399.

TREATMENT OF LIVER AND BILIARY TRACT DISORDERS

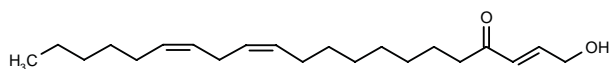
320328

1-Hydroxyhenicosa-2(*E*),5(*E*),12(*Z*),15(*Z*)-tetraen-4-one

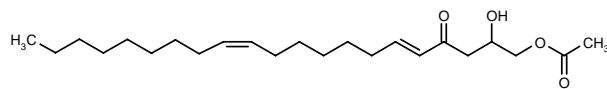


C21 H34 O2; Mol wt: 318.4976

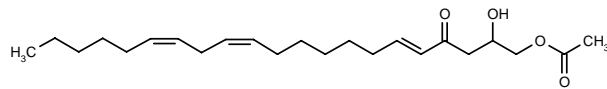
ACTION – Hepatoprotectant that may be obtained by chemical synthesis or isolated from a plant belonging to the avocado family. It demonstrated *in vivo* efficacy in a rat model of chronic hepatitis induced by D-galactosamine following intraduodenal administration at a dose of 100 mg/kg. Other exemplified compounds are:



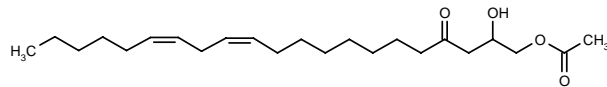
320329: C21 H36 O2



320330: C23 H40 O4



320331: C23 H38 O4



320332: C23 H40 O4

SOURCE – Kagome.

REFERENCES

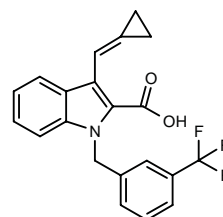
1. Arimoto, Y. et al. (Kagome Co., Ltd.) *Novel hepatopathy inhibitors*. JP 2002105017.

ENDOCRINE DRUGS

ANTIDIABETIC DRUGS

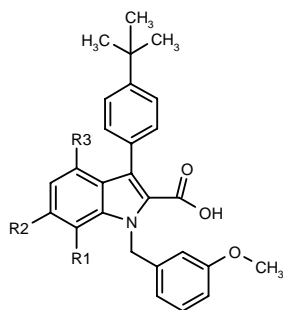
320593

3-(Cyclopropylidenemethyl)-1-[3-(trifluoromethyl)benzyl]-1*H*-indole-2-carboxylic acid

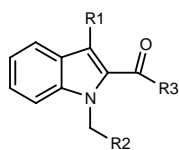


C21 H16 F3 N O2; Mol wt: 371.3564

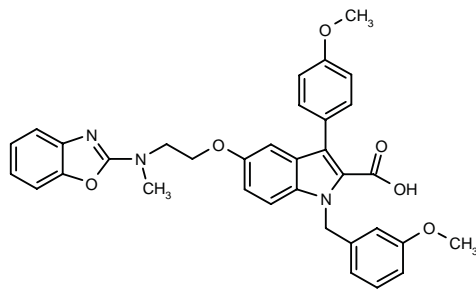
ACTION – Peroxisome proliferator-activated receptor PPAR γ modulator, proven to inhibit the binding of [3 H]-BRL-49653 to PPAR γ receptors with an IC₅₀ of < 10 nM. Potentially useful for the treatment of osteopenia, cancer, hyperglycemia, diabetes, syndrome X, insulin resistance, dyslipidemia, hypertriglyceridemia, hypercholesterolemia and hyperlipidemia, inflammation, atherosclerosis, inflammatory bowel disease, Alzheimer's disease, rheumatoid arthritis, hypertension, obesity, skin disorders and lupus erythematosus. Other specifically claimed substituted indoles are:



Compound	R1	R2	R3	Formula
320595	H	cyclopropyl- -CH ₂ O	H	C ₃₁ H ₃₃ NO ₄
320597	H	H	cyclopropyl- -CH ₂ O	C ₃₁ H ₃₃ NO ₄
320598	cyclopropyl- -NHCONH	H	H	C ₃₁ H ₃₃ N ₃ O ₄



Compound	R1	R2	R3	Formula
320599	4-morpholinyl-CO	3-CF ₃ -Ph	OH	C ₂₂ H ₁₉ F ₃ N ₂ O ₄
320600	2-benzothieryl	3-CF ₃ -Ph	OH	C ₂₅ H ₁₆ F ₃ NO ₂ S
320601	4-MeO-Ph	COPh	OH	C ₂₄ H ₁₉ NO ₄
320602	4-MeO-Ph	3-CF ₃ -Ph	NHSO ₂ Ph	C ₃₀ H ₂₃ F ₃ N ₂ O ₄ S



320596: C₃₄ H₃₁ N₃ O₆

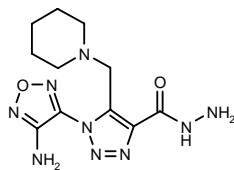
SOURCE – Bayer.

REFERENCES

1. Stolle, A. et al. (Bayer Corp.) *Subst. indoles, pharmaceutical compsns. containing such indoles and their use as PPAR-γ binding agents*. WO 0230895.

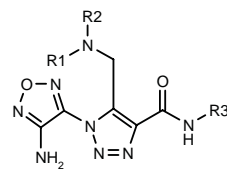
320652

1-(4-Amino-1,2,5-oxadiazol-3-yl)-5-(piperidin-1-ylmethyl)-1H-1,2,3-triazole-4-carbohydrazide

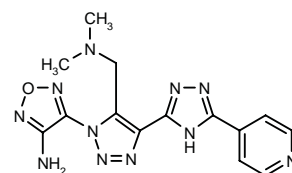


C₁₁ H₁₇ N₉ O₂; Mol wt: 307.3163

ACTION – Glycogen synthase kinase-3 (GSK-3) inhibitor (IC₅₀ < 10 μM), potentially useful for the treatment of hyperglycemia, impaired glucose tolerance, type 1 and type 2 diabetes, Alzheimer's disease and bipolar disorder. Other exemplified furazanyl-triazole derivatives are:



Compound	R1	R2	R3	Formula
320653	-(CH ₂) ₅ -	4-Pyr-CH ₂ CH ₂		C ₁₈ H ₂₃ N ₉ O ₂
320654	-CH ₂ CH ₂ N(Me)CH ₂ CH ₂ -	4-Pyr-CH ₂ CH ₂		C ₁₈ H ₂₄ N ₁₀ O ₂
320655	-(CH ₂) ₅ -	4-F-PhCH ₂ CH ₂		C ₁₉ H ₂₃ FN ₉ O ₂
320657	Et	Et	4-OH-PhC(Me)=N	C ₁₈ H ₂₃ N ₉ O ₃
320658	-CH ₂ CH ₂ OCH ₂ CH ₂ -	N=CHCH=CHMe		C ₁₄ H ₁₉ N ₉ O ₃
320659	-(CH ₂) ₅ -	3-OH-PhCH=N		C ₁₈ H ₂₁ N ₉ O ₃



320656: C₁₄ H₁₅ N₁₁ O

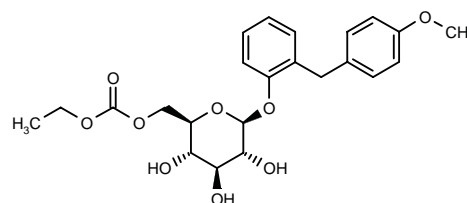
SOURCE – Novo Nordisk.

REFERENCES

1. Olesen, P.H. et al. (Novo Nordisk A/S) *Furazanyl-triazole derivatives for the treatment of diseases*. WO 0232896.

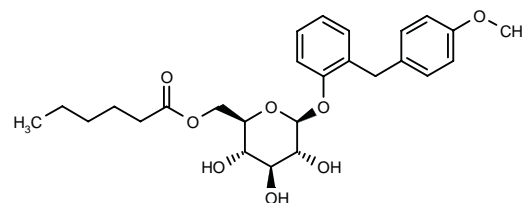
320829

6-O-(Ethoxycarbonyl)-1-O-[2-(4-methoxybenzyl)phenyl]-β-D-glucopyranoside



C₂₃ H₂₈ O₉; Mol wt: 448.4652

ACTION – Orally available prodrug of a known inhibitor of the sodium-dependent glucose transporter SGLT2. It dose-dependently increased urinary glucose excretion following oral administration to rats at doses of 3-30 mg/kg. Compound demonstrated 46% oral bioavailability in rats (10 mg/kg), and caused no deaths in acute toxicity tests in mice at up to 600 mg/kg p.o. Potentially useful for the treatment of diabetes, diabetic complications and obesity, among other disorders associated with hyperglycemia. Another exemplified compound is:



320830: C₂₆ H₃₄ O₈

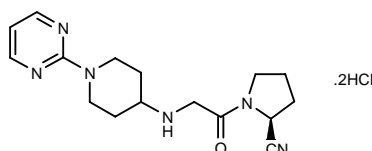
SOURCE – Kissei.

REFERENCES

1. Fujikura, H. et al. (Kissei Pharmaceutical Co., Ltd.) *Glucopyranosyloxybenzyl-benzene derivs. and medicinal compns. containing the same*. WO 0228872.

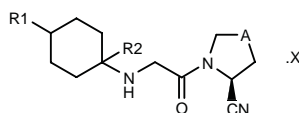
320849

1-[2-[1-(2-Pyrimidinyl)piperidin-4-ylamino]acetyl]pyrrolidine-2(S)-carbonitrile dihydrochloride

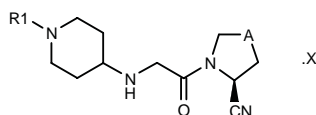


C16 H22 N6 O . 2HCl; Mol wt: 387.3126

ACTION – Dipeptidyl-peptidase IV (DPP-IV) inhibitor, potentially useful for the treatment of diabetes, hyperglycemia, hyperinsulinemia, diabetic complications, obesity, hyperlipidemia and hypertriglyceridemia, arthritis, osteoporosis, AIDS and transplant rejection. Other exemplified compounds are:



Compound	R1	R2	A	Isomer	X	Formula
320851	4-morpholinyl	Me	CH2	cis	2HCl	C ₁₈ H ₃₀ N ₄ O ₂ ·2HCl
320852	4-morpholinyl-CO2	H	CH2	trans	HCl	C ₁₈ H ₂₈ N ₄ O ₄ ·HCl
320856	NHCONHPh	H	CH2	trans	HCl	C ₂₀ H ₂₇ N ₅ O ₂ ·HCl
320858	5-Cl-2-pyrimidinyl-NHCH2	H	CH2	trans	2HCl	C ₁₈ H ₂₅ ClN ₆ O ₂ ·2HCl
320862	5-NO2-2-Pyr-NHCH2	H	S	trans	2HCl	C ₁₈ H ₂₄ N ₆ O ₃ S·2HCl



Compound	R1	A	X	Formula
320854	CONHCH2Ph	CH2	HCl	C ₂₀ H ₂₇ N ₅ O ₂ ·HCl
320860	2-pyrimidinyl	S	2HCl	C ₁₅ H ₂₀ N ₆ O ₃ S·2HCl

SOURCE – Tanabe Seiyaku.

REFERENCES

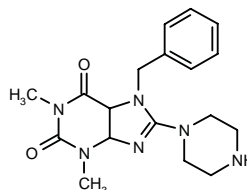
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BDPX

320990

7-Benzyl-1,3-dimethyl-8-(1-piperazinyl)-2,3,4,5,6,7-hexahydro-1H-purine-2,6-dione

7-Benzyl-1,3-dimethyl-8-(1-piperazinyl)xanthine



C18 H24 N6 O2; Mol wt: 356.4276

ACTION – Potent and competitive inhibitor of human dipeptidyl-peptidase IV with favorable pharmacokinetic properties in rats and active in an oral glucose tolerance test in the Zucker obese rat model. Potentially useful for the treatment of type 2 diabetes.

SOURCE – Novo Nordisk.

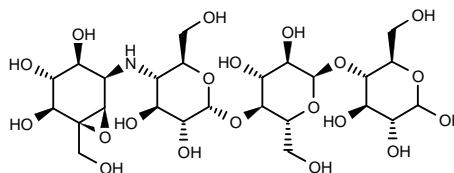
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CKD-711

298541

4-Deoxy-4-[(1R,2R,3S,4R,5S,6S)-3,4,5-trihydroxy-6-(hydroxymethyl)-7-oxabicyclo[4.1.0]hept-2-ylamino]-α-D-glucopyranosyl-(1→4)-α-D-glucopyranosyl-(1→4)-D-glucopyranose



C25 H43 N O20; Mol wt: 677.6017

ACTION – Amino-oligosaccharide α-glucosidase inhibitor produced by a culture broth of *Streptomyces* sp. CK-4416, a soil microorganism found in South Korea. The compound inhibited porcine intestinal maltase (IC₅₀ = 2.5 μg/ml) and sucrase (IC₅₀ = 0.5 μg/ml), but was less effective against α-amylase activity (IC₅₀ = 78.0 μg/ml), suggesting potential for reduced side effects such as abdominal distension, flatulence, meteorism and diarrhea associated with inhibition of amylase. *In vivo*, like acarbose, it inhibited the increase in blood glucose levels in starch- and sucrose-fed rats with ED₅₀ values of 3.1 and 1.1 mg/kg p.o., respectively. No toxicity was observed in rats up to 10,000 mg/kg p.o., nor following 4 weeks of treatment at doses up to 1000 mg/kg/day. Potentially useful for the treatment of diabetes.

SOURCE – Chong Kun Dang.

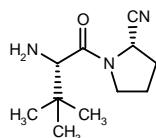
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FE-999011

320372

1-(3-Methyl-L-valyl)pyrrolidine-2(S)-carbonitrile



C₁₁ H₁₉ N₃ O; Mol wt: 209.2911

ACTION – Potent and reversible inhibitor of dipeptidyl-peptidase IV (DPP-IV; $K_i = 0.88 \mu\text{M}$) able to produce significant and long-lasting reductions in plasma DPP-IV activity in Zucker fatty rats at a dose of 10 mg/kg p.o. and to dose-dependently (1-10 mg/kg) reduce plasma glucose excursions during an oral glucose tolerance test. Chronic oral treatment with a dose of 10 mg/kg b.i.d. for 7 days also improved glucose tolerance in Zucker fatty rats, while having no effect on food and water intake or body weight gain. In Zucker diabetic fatty (ZDF) rats, a dose of 10 mg/kg p.o. once or twice daily significantly delayed (21 days) the development of hyperglycemia, stabilized food and water intake to normal levels and attenuated the increases in plasma triglyceride and free fatty acid levels. These effects were associated with significant elevations in plasma GLP-1 levels and pancreatic GLP-1 receptor gene expression. Potentially useful for the treatment of type 2 diabetes.

SOURCE – Ferring.

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HIM2

282659

Conjugate of the hexyl oligomer $[\text{CH}_3\text{O}-(\text{PEG})_n-\text{O}(\text{CH}_2)_5\text{COOH}$, $n = 7-9$] covalently attached at the lysine 29 site on the B-chain of recombinant human insulin

Modified human recombinant insulin by the conjugation of the oligomer methoxy(polyethylene glycol)hexanoic acid to the B29-Lys of human insulin

Hexyl insulin M2

Hexyl-insulin monoconjugate 2

NIN-058

ACTION – Orally active recombinant human insulin conjugated with an amphiphilic oligomer, currently in phase II clinical development for both type 1 and type 2 diabetes. In dogs, the conjugate given i.v. provided significantly reduced clearance and increased overall exposure compared with unmodified insulin. In adult patients with type 1 diabetes, the oral conjugate (0.25 mg/kg) exhibited maximal absorption and efficacy when given 15 min prior to a meal. In type 2 diabetic patients, the dose of 1 mg/kg p.o. before a standard meal resulted in postprandial glucose control similar to that with s.c. insulin-lispro (8 U).

SOURCES – GlaxoSmithKline; Nobex.

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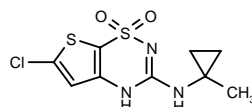
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NN-414*

291833

6-Chloro-3-(1-methylcyclopropylamino)-4H-thieno[3,2-e]-[1,2,4]thiadiazine-1,1-dioxide



C₉H₁₀ClN₃O₂S₂; Mol wt: 291.7820

ACTION – Diazoxide analogue, a potent and selective pancreatic β -cell K(ATP) SUR1/Kir6.2 channel opener ($EC_{50} = 0.3\text{--}0.5\ \mu\text{M}$ in HEK293 cells stably expressing human channels) able to prevent glucose-induced β -cell apoptosis and to decrease chronic insulin secretion in cultured human pancreatic islets. In Zucker obese rats, compound was 20-fold more potent than diazoxide in reducing plasma insulin levels in an acute study ($ID_{50} = 1.5\ \text{mg/kg p.o.}$) and was devoid of cardiovascular effects; in chronic studies it significantly reduced postprandial glycemia, and also attenuated the increase in hyperinsulinemia and the deterioration of glucose intolerance. Results from a phase I clinical study in healthy volunteers showed that single oral doses of 0.625–12.5 mg/kg were generally well tolerated, and plasma profiles showed a t_{\max} of 0.5–2 h and a terminal elimination half-life of 10–20 h. In this study, compound inhibited insulin secretion at 1 h after administration, and improved glucose tolerance and β -cell secretory function, although it was not associated with a clinically significant effect on insulin sensitivity. In another study, multiple doses (1.5, 4.5 or 10 mg/kg once daily for 7 days) were investigated in type 2 diabetes patients. No clinically relevant changes in vital signs, ECG or laboratory parameters were seen; a significant and selective inhibition of insulin secretion and an increase in plasma glucose levels were observed at 1 h after administration. Glucose tolerance and β -cell secretory function were improved throughout the study. Potentially useful for the treatment of type 2 diabetes.

SOURCE – Novo Nordisk.

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*Identified compound **291833** (see **291831**) Drug Data Rep 2000, 022(11): 1007.

hOKT3 γ 1(Ala-Ala)

284958

Genetically engineered derivative of the murine OKT3 monoclonal antibody, in which the six complementarity-determining regions have been grafted within a human IgG, MAb and the amino acids at positions 234 and 235 have been mutated to alanine residues to alter FcR-binding activity

HuOKT3 γ 1(Ala234-Ala235)

ACTION – Non-Fc receptor-binding humanized anti-CD3 monoclonal antibody that contains the binding region of OKT3 and a mutated binding region of the Fc region that prevents it from binding to the Fc receptor, proven to reduce OKT3 side effects in renal allograft patients. Results from a phase I/II clinical trial in patients with type 1 diabetes showed that 9 of 12 patients treated with the antibody maintained or improved their insulin production after 1 year compared to 2 of 12 control patients. Treated patients also exhibited improvement in other clinical signs of diabetes such as glycosylated hemoglobin levels and insulin doses; an increase in the absolute number of CD8⁺ T-cells, resulting in a reduction in the ratio of CD4⁺ T-cells to CD8⁺ T-cells at 3 months, was also seen. The antibody was well tolerated by all patients and the most common side effects included fever, rash and anemia.

SOURCES – University of California, San Francisco, CA (US) Columbia University, New York, NY (US); R.W. Johnson.

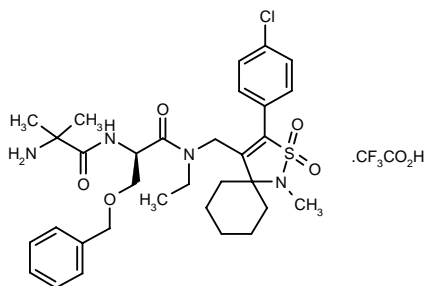
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TREATMENT OF GROWTH HORMONE SECRETION DISORDERS

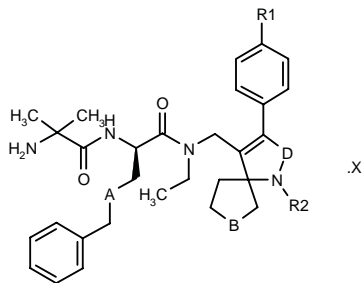
320729

*N*²-(2-Methylalanyl)-*O*-benzyl-*N*¹-[3-(4-chlorophenyl)-1-methyl-2,2-dioxo-2-thia-1-azaspiro[4.5]dec-3-en-4-ylmethyl]-*N*¹-ethyl-D-serinamide trifluoroacetate



C32 H43 Cl N4 O5 S . C2 H F3 O2; Mol wt: 745.2556

ACTION – Growth hormone secretagogue with potential in the treatment of disorders associated with growth hormone deficiency such as osteoporosis and loss of muscle strength, either alone or in combination with a bone antiresorptive agent. Other exemplified substituted peptides are:



Compound	R1	R2	A	B	D	X	Formula
320730	t-Bu	H	O	-(CH2)2-	SO2	CF3CO2H	C ₃₅ H ₅₀ N ₄ O ₅ S .C ₂ HF ₃ O ₂
320731	H	Me	O	-(CH2)2-	SO2	HCl	C ₃₂ H ₄₄ N ₄ O ₅ S.HCl
320732	NO2	Me	O	-(CH2)2-	SO2	HCl	C ₃₂ H ₄₃ N ₅ O ₇ S.HCl
320733	F	H	CH2	-(CH2)2-	SO2	CF3CO2H	C ₃₂ H ₄₃ FN ₄ O ₄ S .C ₂ HF ₃ O ₂
320734	H	H	O	-CH2-	SO2	HCl	C ₃₀ H ₄₀ N ₄ O ₅ S.HCl
320735	Cl	H	O	-(CH2)2-	CO	HCl	C ₃₂ H ₄₁ ClN ₄ O ₄ .HCl
320737	Cl	Me	O	-(CH2)2-	CO	CF3CO2H	C ₃₃ H ₄₃ ClN ₄ O ₄ .C ₂ HF ₃ O ₂
320738	SO2Me	H	O	-(CH2)2-	SO2	CF3CO2H	C ₃₂ H ₄₄ N ₄ O ₇ S ₂ .C ₂ HF ₃ O ₂

SOURCE – Lilly.

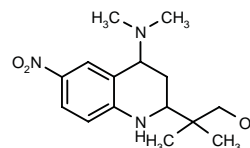
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TREATMENT OF MALE SEXUAL DYSFUNCTION

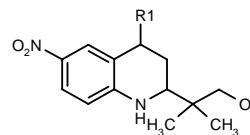
319767

2-[4-(Dimethylamino)-6-nitro-1,2,3,4-tetrahydroquinolin-2-yl]-2-methylpropan-1-ol



C15 H23 N3 O3; Mol wt: 293.3647

ACTION – Androgen receptor modulator shown to bind to androgen receptors in rat prostate homogenates. *In vivo*, compound induced prostate weight gain following administration to hemicastrated rats (30 mg/kg/day s.c. for 8 days) and an increase in bone mineral density in either hemicastrated or ovariectomized rats (30 mg/kg/day s.c. 5 days per week during 4 weeks). Potentially useful for the treatment of male hypogonadism, male reproductive dysfunction and sterility, delayed male puberty, hypoplastic, hemolytic and sickle cell anemia, thrombocytopenic purpura, myelofibrosis, renal anemia, osteoporosis, breast cancer, mastopathy, endometriosis and female reproductive dysfunction. Its use in the treatment of androgen-mediated disorders such as prostatic cancer and hypertrophy, virilism, acne, seborrhea, hypertrichosis and polycystic ovary syndrome is also described. Other exemplified 1,2,3,4-tetrahydroquinoline derivatives are:



Compound	R1	Formula
319768	OEt	C ₁₅ H ₂₂ N ₂ O ₄
319769	SEt	C ₁₅ H ₂₂ N ₂ O ₃ S
319770	SPh	C ₁₉ H ₂₂ N ₂ O ₃ S
319771	NHCH2Ph	C ₂₀ H ₂₅ N ₃ O ₃
319772	N(Pr)2	C ₁₉ H ₃₁ N ₃ O ₃

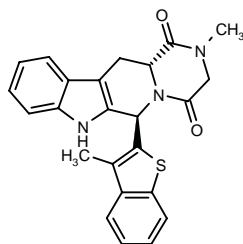
SOURCE – Kaken.

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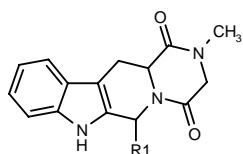
319787

(6*R*,12*aR*)-2-Methyl-6-(3-methyl-1-benzothien-2-yl)-1,2,3,4,6,7,12,12*a*-octahydropyrazino[1',2':1,6]pyrido-[3,4-*b*]indole-1,4-dione



C₂₄ H₂₁ N₃ O₂ S; Mol wt: 415.5149

ACTION – Potent and selective phosphodiesterase type 5 (PDE5) inhibitor (IC₅₀ = 1 nM). Potentially useful for the treatment of male erectile dysfunction and female arousal disorder. Other exemplified compounds are:



Compound	R1	Isomer	Formula
319790	2-benzofuryl	6 <i>S</i> ,12 <i>aR</i>	C ₂₃ H ₁₉ N ₃ O ₃
319792	3-Me-2-benzothienyl	6 <i>R</i> ,12 <i>aS</i>	C ₂₄ H ₂₁ N ₃ O ₂ S
319793	3-Me-2-benzothienyl	6 <i>S</i> ,12 <i>aS</i>	C ₂₄ H ₂₁ N ₃ O ₂ S
319795	thieno[2,3- <i>b</i>]furan-5-yl	6 <i>S</i> ,12 <i>aR</i>	C ₂₁ H ₁₇ N ₃ O ₃ S

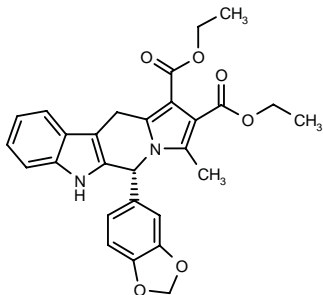
SOURCE – Lilly Icos.

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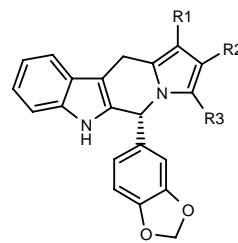
319797

5(*R*)-(1,3-Benzodioxol-5-yl)-3-methyl-6,11-dihydro-5*H*-indolizino[6,7-*b*]indole-1,2-dicarboxylic acid diethyl diester

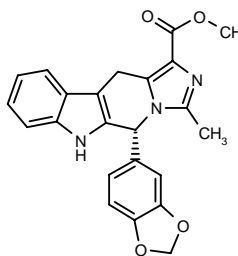


C₂₈ H₂₆ N₂ O₆; Mol wt: 486.5214

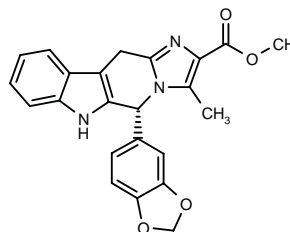
ACTION – Potent and selective phosphodiesterase type 5 (PDE5) inhibitor (IC₅₀ = 0.0056 nM). Potentially useful for the treatment of male erectile dysfunction and female arousal disorder. Other specifically claimed compounds are:



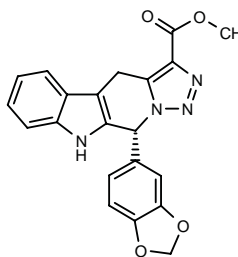
Compound	R1	R2	R3	Formula
319801	CN	(CH ₂) ₄ CO ₂ H	Me	C ₂₈ H ₂₅ N ₃ O ₄
319802	CO ₂ Et	H	Et	C ₂₈ H ₂₄ N ₂ O ₄
319803	CONH ₂	CONH ₂	H	C ₂₃ H ₁₈ N ₄ O ₄
319804	CONH ₂	CONH ₂	CF ₃	C ₂₄ H ₁₇ F ₃ N ₄ O ₄



319798: C₂₃ H₁₉ N₃ O₄



319799: C₂₃ H₁₉ N₃ O₄



319800: C₂₁ H₁₆ N₄ O₄

SOURCE – Lilly Icos.

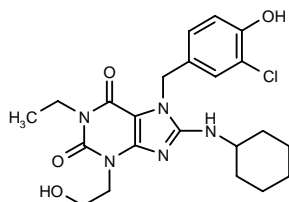
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1. Orme, M.W. et al. (Lilly Icos LLC) *Chemical cpds.* WO 0228859.

320085

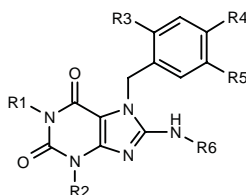
7-(3-Chloro-4-hydroxybenzyl)-8-(cyclohexylamino)-1-ethyl-3-(2-hydroxyethyl)-2,3,6,7-tetrahydro-1*H*-purine-2,6-dione

7-(3-Chloro-4-hydroxybenzyl)-8-(cyclohexylamino)-1-ethyl-3-(2-hydroxyethyl)xanthine



C₂₂H₂₈ClN₅O₄; Mol wt: 461.9472

ACTION – Phosphodiesterase type 5 (PDE5) inhibitor for the treatment of erectile dysfunction, as well as other PDE5-related disorders including angina pectoris, hypertension, postangioplasty restenosis, stroke, diabetes, polycystic ovary syndrome, nephritis, glaucoma, cachexia and cancer. Other exemplified xanthine derivatives are:



Compound	R1	R2	R3	R4	R5	R6	Formula
320086	Et	CH ₂ CH ₂ OH	H	OMe	Br	2(R)-OH-1(R)-cyclopentyl	C ₂₂ H ₂₈ BrN ₅ O ₅
320087	Me	Me	Cl	-OCH ₂ O-	cyclohexyl		C ₂₁ H ₂₄ ClN ₅ O ₄

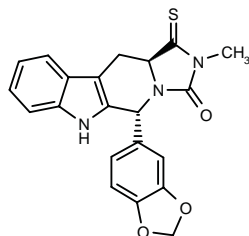
SOURCE – Schering-Plough.

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1. Chackalamannil, S. et al. (Schering Corp.) *Xanthine phosphodiesterase V inhibitors*. WO 0224698.

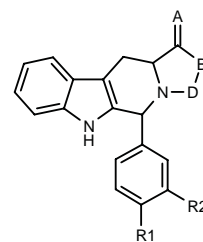
320159

(5*R*,11*aS*)-5-(1,3-Benzodioxol-5-yl)-2-methyl-1-thioxo-2,3,5,6,11,11*a*-hexahydro-1*H*-imidazo[1',5':1,6]pyrido-[3,4-*b*]indol-3-one



C₂₁H₁₇N₃O₃S; Mol wt: 391.4493

ACTION – Phosphodiesterase type 5 (PDE5) inhibitor (IC₅₀ = 12 nM), potentially useful for the treatment of a broad range of PDE5-mediated disorders, particularly male erectile dysfunction and female arousal disorder. Other exemplified compounds are:



Compound	R1	R2	A	B	D	Isomer	Formula
320160	-OCH ₂ O-		O	O	CO	(+)-5 <i>R</i> ,11 <i>aR</i>	C ₂₀ H ₁₄ N ₂ O ₅
320161	-OCH ₂ O-		O	O	CS	5 <i>R</i> ,11 <i>aR</i>	C ₂₀ H ₁₄ N ₂ O ₄ S
320162	-OCH ₂ O-		O	N(Me)	CS	5 <i>R</i> ,11 <i>aS</i>	C ₂₁ H ₁₇ N ₃ O ₃ S
320163	OMe	H	O	N(Bu)	CS	(+)-5 <i>S</i> ,11 <i>aS</i>	C ₂₄ H ₂₅ N ₃ O ₂ S
320164	-OCH ₂ O-		O	CH ₂	CO		C ₂₁ H ₁₆ N ₂ O ₄
320165	-OCH ₂ O-		H ₂	N(Me)	CO	(+)-5 <i>S</i> ,11 <i>aS</i>	C ₂₁ H ₁₉ N ₃ O ₃
320166	OMe	H	O	N(CH ₂ Ph)	CH ₂	(+)-5 <i>R</i> ,11 <i>aS</i>	C ₂₇ H ₂₅ N ₃ O ₂
320167	-OCH ₂ O-		H ₂	O	CO		C ₂₀ H ₁₆ N ₂ O ₄
320168	-OCH ₂ O-		O	CH ₂	CH ₂	(+)-5 <i>R</i> ,11 <i>aR</i>	C ₂₁ H ₁₈ N ₂ O ₃
320169	-OCH ₂ O-		H ₂	O	SO		C ₁₉ H ₁₆ N ₂ O ₄ S

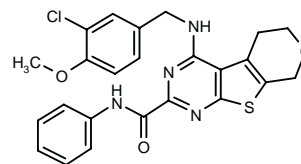
SOURCE – Lilly Icos.

REFERENCES

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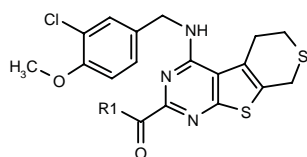
320825

4-(3-Chloro-4-methoxybenzylamino)-*N*-phenyl-6,8-dihydro-5*H*-pyrano[4',3':4,5]thieno[2,3-*d*]pyrimidine-2-carboxamide



C₂₄H₂₁ClN₄O₃S; Mol wt: 480.9739

ACTION – Selective inhibitor of cGMP-specific phosphodiesterase (PDE) with an IC₅₀ of 0.51 nM against PDE5 and 20,000-fold selectivity over PDE1 and PDE4. Potentially useful for the treatment of impotence, hypertension, heart failure, myocardial infarction, angina pectoris, arteriosclerosis, restenosis following PTCA, cardiac, renal or pulmonary edema, pulmonary hypertension, renal failure, asthma, bronchitis, dementia, immunodeficiency and glaucoma. Other exemplified condensed thieno[2,3-*d*]pyrimidine derivatives are:



Compound	R1	Formula
320826	OEt	C ₂₀ H ₂₀ ClN ₃ O ₃ S ₂
320827	NHPh	C ₂₄ H ₂₁ ClN ₄ O ₂ S ₂
320828	2-thiazolyl-NH	C ₂₁ H ₁₈ ClN ₅ O ₂ S ₃

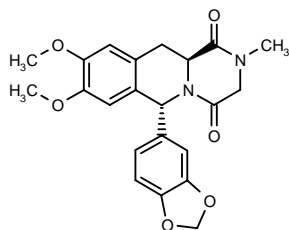
SOURCE – Nippon Soda.

REFERENCES

1. Umeda, N. et al. (Nippon Soda Co., Ltd.) *Condensed thienopyrimidine cpds., their salts and preparation method.* JP 2002105082.

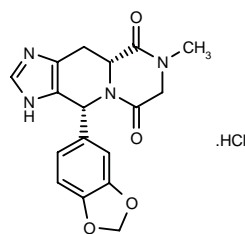
321043

(6*R*,11*aS*)-6-(1,3-Benzodioxol-5-yl)-8,9-dimethoxy-2-methyl-2,3,4,6,11,11*a*-hexahydro-1*H*-pyrazino[1,2-*b*]-isoquinoline-1,4-dione



C₂₂ H₂₂ N₂ O₆; Mol wt: 410.4238

ACTION – Potent and selective inhibitor of cGMP-specific phosphodiesterases, particularly PDE5 (IC₅₀ = 718 nM), expected to be useful for the treatment of cardiovascular disorders and erectile dysfunction. Another exemplified compound is:



321044: C₁₇ H₁₆ N₄ O₄ . HCl

SOURCE – Lilly Icos.

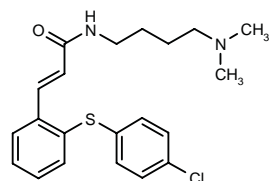
REFERENCES

1. Orme, M.W. et al. (Lilly Icos LLC) *Chemical cpds.* WO 0238563.

A-350619

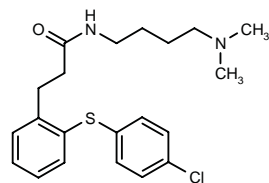
320148

3-[2-(4-Chlorophenylsulfanyl)phenyl]-*N*-[4-(dimethyl-amino)butyl]-2-propenamide



C₂₁ H₂₅ Cl N₂ O S; Mol wt: 388.9605

ACTION – Soluble guanylate cyclase (sGC) activator able to potentiate the effect of the nitric oxide (NO) donor sodium nitroprusside on rat sGC and to relax phenyleprine-precontracted rabbit corpus cavernosus strips with an EC₅₀ value of 14 μM. In rats, compound induced penile erection at a dose of 1 μmol/kg. Potentially useful for the treatment of erectile dysfunction. Another related compound is:



A-344905 [320145]: C₂₁ H₂₇ Cl N₂ O S

SOURCE – Abbott.

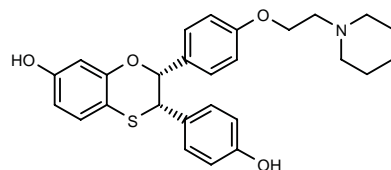
REFERENCES

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TREATMENT OF GYNECOLOGICAL DISORDERS

320522

3(*S*)-(4-Hydroxyphenyl)-2(*R*)-[4-[2-(1-piperidinyl)ethoxy]-phenyl]-2,3-dihydro-1,4-benzoxathiin-7-ol



C₂₇ H₂₉ N O₄ S; Mol wt: 463.5951

ACTION – A representative compound within a series of estrogen receptor ERα agonists, potentially useful for the treatment of postmenopausal osteoporosis, as well as estrogen-dependent breast cancer, uterine fibrosis, restenosis, endometriosis and hyperlipidemia.

SOURCE – Merck & Co.

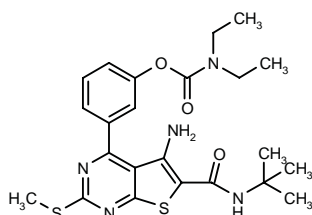
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1. Dininno, F.P. et al. (Merck & Co., Inc.) *Estrogen receptor modulators*. WO 0232373.
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AGENTS FOR FEMALE INFERTILITY

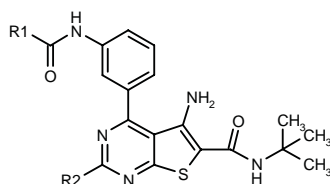
319679

N,N-Diethylcarbamic acid 3-[5-amino-6-(*N*-*tert*-butyl-carbamoyl)-2-(methylsulfanyl)thieno[2,3-*d*]pyrimidin-4-yl]phenyl ester



C₂₃ H₂₉ N₅ O₃ S₂; Mol wt: 487.6461

ACTION – Luteinizing hormone (LH) agonist, potentially useful for the control of fertility. Compound displayed EC₅₀ values below 10 nM at LH receptors expressed in CHO cells. Other exemplified bicyclic heteroaromatic compounds are:



Compound	R1	R2	Formula
319680	OMe	SMe	C ₂₀ H ₂₃ N ₅ O ₃ S ₂
319681	allyl-O	SMe	C ₂₂ H ₂₆ N ₅ O ₃ S ₂
319682	OEt	SMe	C ₂₁ H ₂₆ N ₅ O ₃ S ₂
319683	4-morpholinyl	SMe	C ₂₃ H ₂₈ N ₆ O ₃ S ₂
319687	1,2,5,6-tetrahydro-1-Pyr	SMe	C ₂₄ H ₂₈ N ₆ O ₂ S ₂
319689	N(Me) ₂	Ph	C ₂₆ H ₂₈ N ₆ O ₂ S

SOURCE – Akzo Nobel.

REFERENCES

1. Timmers, C.M. and Karstens, W.F.J. (Akzo Nobel N.V.) *Bicyclic heteroaromatic cpds*. WO 0224703.

CONTRACEPTIVES

NORELGESTROMIN/ETHINYL-ESTRADIOL

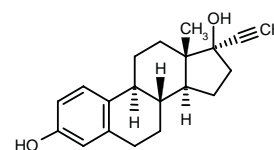
New combination

298406

Combination of norelgestromin and ethinylestradiol

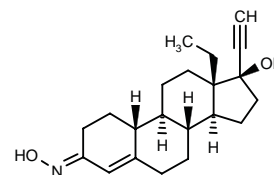
Evra™

Ethinyl estradiol
125559



C₂₀ H₂₄ O₂; Mol wt: 296.4130

Norelgestromin
300721



C₂₁ H₂₉ N O₂; Mol wt: 327.4651

ACTION – Transdermal contraceptive, a combination of the progestin norelgestromin and the estrogen ethinylestradiol, that acts primarily by suppressing ovulation.

INDICATION – Prevention of pregnancy.

PRESENTATION – Seve-day transdermal patches containing 6.0 mg norelgestromin and 0.75 mg ethinylestradiol, releasing 150 µg norelgestromin and 20 µg ethinylestradiol into the bloodstream per 24 h.

PROPRIETARY NAME – Ortho Evra (US).

SOURCE – Ortho-McNeil.

REFERENCES

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2. Jona, J. et al. (Cygnus, Inc.) *Transdermal patch and method for administering 17-deacetyl norgestimate alone or in combination with an estrogen*. US 5972377.
3. Li, C. et al. (Cygnus, Inc.) *Pressure sensitive acrylate adhesive compsn. cross-linked with aluminum acetyltonate and containing a drug having a reactive aromatic hydroxyl group*. WO 9640087.
4. Abrams, L. et al. *Bioavailability of 17-deacetylnorgestimate (17D-NGM) and ethinyl estradiol (EE) from a contraceptive patch*. FASEB J 2000, 14(8): Abst 961.
5. Abrams, L.S. et al. *Multiple-dose pharmacokinetics of a contraceptive patch in healthy women participants*. Contraception 2001, 64: 287.
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8. Abrams, L.S. et al. *Pharmacokinetics of norelgestromin and ethinyl estradiol from two consecutive contraceptive patches*. J Clin Pharmacol 2001, 41(11): 1232.

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10. Archer, D. et al. *An integrated assessment of patient compliance with a weekly contraceptive patch (ORTHO EVRA™/EVRA™)*. Fertil Steril 2001, 76(3, Suppl. 1): Abst O-50.

11. Archer, D.F. et al. *Assessment of compliance with a weekly contraceptive patch (Ortho Evra™/Evra™) among North American women*. Fertil Steril 2002, 77(2): S27.

12. Dittich, R. et al. *Transdermal contraception: Evaluation of three transdermal norelgestromin/ethinyl estradiol doses in a randomized, multicenter, dose-response study*. Am J Obstet Gynecol 2002, 186(1): 15.

13. Roach, J. et al. *Evaluation of skin irritation in humans from a contraceptive patch*. FASEB J 2000, 14(8): Abst 178.

14. Sibai, B. et al. *A comparative assessment of ORTHO EVRA™/EVRA™ to placebo patch effects on body weight*. Fertil Steril 2001, 76(3, Suppl. 1): Abst P-225.

15. Sibai, B.M. et al. *A comparative and pooled analysis of the safety and tolerability of the contraceptive patch (Ortho Evra™/Evra™)*. Fertil Steril 2002, 77(2): S19.

16. Thorne, E.G. et al. *Lack of phototoxicity and photoallergy with a contraceptive patch*. FASEB J 2000, 14(8): Abst 179.

17. Zacur, H. et al. *Integrated summary of ORTHO EVRA™/EVRA™ contraceptive patch adhesion in varied climates and conditions*. Fertil Steril 2001, 76(3, Suppl. 1): Abst O-49.

18. Zieman, M. et al. *Contraceptive efficacy and cycle control with the Ortho Evra™/Evra™ transdermal system: The analysis of pooled data*. Fertil Steril 2002, 77(2): S13.

19. Zieman, M. et al. *Integrated summary of contraceptive efficacy with the ORTHO EVRA™/EVRA™ transdermal system*. Fertil Steril 2001, 76(3, Suppl. 1): Abst O-48.

20. *FDA grants approval for the first birth control patch*. DailyDrugNews.com (Daily Essentials) 2001, Nov 23.

21. *First birth control patch Ortho Evra launched* Daily. DrugNews.com (Daily Essentials) 2002, May 2.

22. *Ortho-McNeil to acquire Cygnus drug delivery assets*. DailyDrugNews.com (Daily Essentials) 1999, Nov 29.

23. *Positive opinion handed down by CPMP for EVRA*. DailyDrugNews.com (Daily Essentials) 2002, Feb 27.

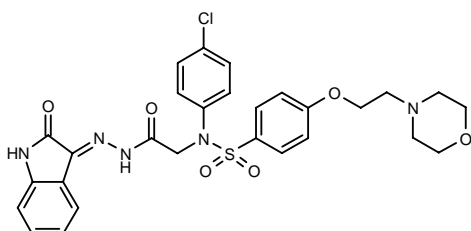
24. *R.W. Johnson seeks FDA approval for transdermal contraceptive*. DailyDrugNews.com (Daily Essentials) 2000, Dec 28.

UTERINE STIMULANTS AND TOCOLYTICS

320660

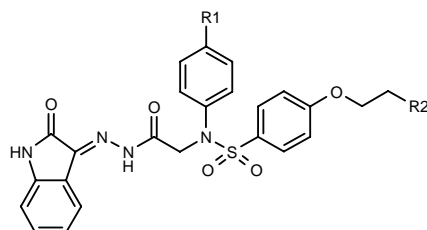
N-(4-Chlorophenyl)-4-[2-(4-morpholinyl)ethoxy]-*N*-(2-oxo-2,3-dihydro-1*H*-indol-3-ylidene)carbazoylethylmethylbenzenesulfonamide

2-[*N*-(4-Chlorophenyl)-*N*-(4-[2-(4-morpholinyl)ethoxy]phenylsulfonyl)amino]-*N'*-(2-oxo-2,3-dihydro-1*H*-indol-3-ylidene)acetohydrazide



C28 H28 Cl N5 O6 S; Mol wt: 598.0772

ACTION – Oxytocin antagonist with high binding affinity for human oxytocin receptors ($K_i = 0.0008 \mu\text{M}$). In functional assays, compound inhibited oxytocin-induced intracellular Ca^{2+} mobilization in HEK cells with an IC_{50} of $0.007 \mu\text{M}$. *In vivo*, it dose-dependently inhibited oxytocin-stimulated uterine contractions following administration to rats, with 71.3% inhibition at a dose of 30 mg/kg. Potentially useful for the treatment of preterm labor, dysmenorrhea, unregulated vasopressin secretion, congestive heart failure, arterial hypertension, liver cirrhosis, nephrotic syndrome and ocular hypertension. Other exemplified compounds are:



Compound	R1	R2	Formula
320661	Cl	CH ₂ N(Me) ₂	C ₂₇ H ₂₈ ClN ₅ O ₆ S
320662	Me	H	C ₂₅ H ₂₄ N ₄ O ₆ S

SOURCE – Applied Research Systems.

REFERENCES

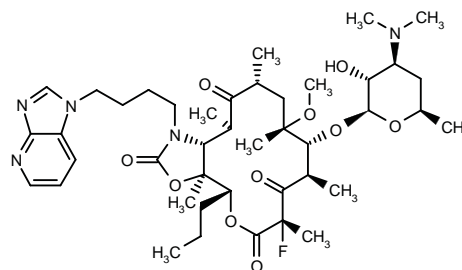
1. Quattropani, A. et al. (Applied Research Systems ARS Holdings NV) *Pharmaceutically active sulfanilide derivs*. WO 0232864.

ANTIINFECTIVE THERAPY

ANTIBIOTICS

320709

13-Deethyl-11-deoxy-3-des(hexopyranosyloxy)-2-fluoro-11-[4-(1*H*-imidazo[4,5-*b*]pyridin-1-yl)butylamino]-6-*O*-methyl-3-oxo-13-propylerythromycin A 11-*N*,12-*O*-cyclic carbamate



C42 H64 F N5 O10; Mol wt: 817.9906

8. Abrams, L.S. et al. *Pharmacokinetics of norelgestromin and ethinyl estradiol from two consecutive contraceptive patches*. J Clin Pharmacol 2001, 41(11): 1232.

9. Abrams, L.S. et al. *Pharmacokinetics of norelgestromin and ethinyl estradiol delivered by a contraceptive patch (Ortho Evra™/Evra™) under conditions of heat, humidity, and exercise*. J Clin Pharmacol 2001, 41(12): 1301.

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20. *FDA grants approval for the first birth control patch*. DailyDrugNews.com (Daily Essentials) 2001, Nov 23.

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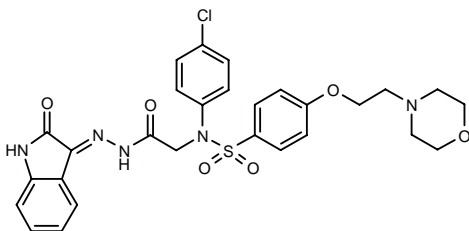
24. *R.W. Johnson seeks FDA approval for transdermal contraceptive*. DailyDrugNews.com (Daily Essentials) 2000, Dec 28.

UTERINE STIMULANTS AND TOCOLYTICS

320660

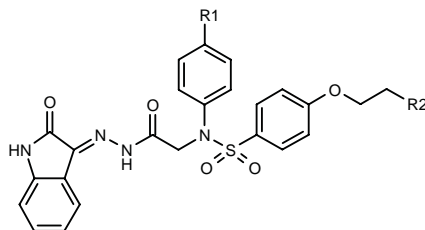
N-(4-Chlorophenyl)-4-[2-(4-morpholinyl)ethoxy]-*N*-[3-(2-oxo-2,3-dihydro-1*H*-indol-3-ylidene)carbazoylmethyl]-benzenesulfonamide

2-[*N*-(4-Chlorophenyl)-*N*-[4-[2-(4-morpholinyl)ethoxy]-phenylsulfonyl]amino]-*N'*-(2-oxo-2,3-dihydro-1*H*-indol-3-ylidene)acetohydrazide



C28 H28 Cl N5 O6 S; Mol wt: 598.0772

ACTION – Oxytocin antagonist with high binding affinity for human oxytocin receptors ($K_i = 0.0008 \mu\text{M}$). In functional assays, compound inhibited oxytocin-induced intracellular Ca^{2+} mobilization in HEK cells with an IC_{50} of $0.007 \mu\text{M}$. *In vivo*, it dose-dependently inhibited oxytocin-stimulated uterine contractions following administration to rats, with 71.3% inhibition at a dose of 30 mg/kg. Potentially useful for the treatment of preterm labor, dysmenorrhea, unregulated vasopressin secretion, congestive heart failure, arterial hypertension, liver cirrhosis, nephrotic syndrome and ocular hypertension. Other exemplified compounds are:



Compound	R1	R2	Formula
320661	Cl	CH2N(Me)2	C ₂₇ H ₂₈ ClN ₅ O ₆ S
320662	Me	H	C ₂₆ H ₂₄ N ₄ O ₆ S

SOURCE – Applied Research Systems.

REFERENCES

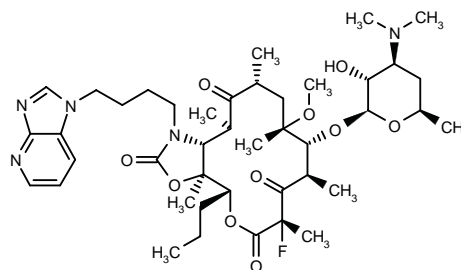
1. Quattropani, A. et al. (Applied Research Systems ARS Holdings NV) *Pharmaceutically active sulfanilide derivs*. WO 0232864.

ANTIINFECTIVE THERAPY

ANTIBIOTICS

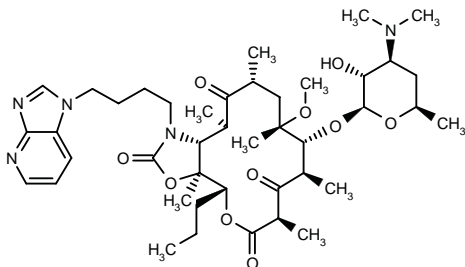
320709

13-Deethyl-11-deoxy-3-des(hexopyranosyloxy)-2-fluoro-11-[4-(1*H*-imidazo[4,5-*b*]pyridin-1-yl)butylamino]-6-*O*-methyl-3-oxo-13-propylerythromycin A 11-*N*,12-*O*-cyclic carbamate



C42 H64 F N5 O10; Mol wt: 817.9906

ACTION – Ketolide antibacterial for the treatment of bacterial and protozoal infections, demonstrated to have *in vitro* activity against *Escherichia coli* OC2605 (MIC = 2 µg/ml), *Staphylococcus aureus* ATCC29213 (MIC = 0.12 µg/ml), *Enterococcus faecalis* ATCC29212 (MIC = 0.03 µg/ml), *Streptococcus pneumoniae* ATCC49619 (MIC < 0.015 µg/ml) and *Haemophilus influenzae* OC4883 (MIC < 0.25 µg/ml). Another exemplified erythromycin analogue is:



320718: C₄₂ H₆₅ N₅ O₁₀

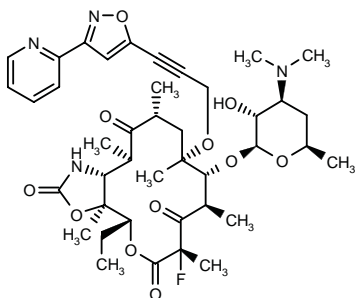
SOURCE – Ortho-McNeil.

REFERENCES

1. Hlasta, D. et al. (Ortho-McNeil Pharmaceutical, Inc.) *Ketolide antibacterials*. WO 0232918.

320803

11-Amino-3-des(hexopyranosyloxy)-11-deoxy-2-fluoro-3-oxo-6-*O*-[3-[3-(2-pyridyl)isoxazol-5-yl]-2-propynyl]-erythromycin A 11-*N*,12-*O*-cyclic carbamate



C₄₁ H₅₅ F N₄ O₁₁; Mol wt: 798.9005

ACTION – Antibacterial 6-*O*-substituted erythromycin A derivative with an improved gastrointestinal tolerability profile. It induced no emesis and minimal nausea when administered to ferrets at a dose of 30 mg/kg p.o., comparing favorably with erythromycin, clarithromycin and telithromycin.

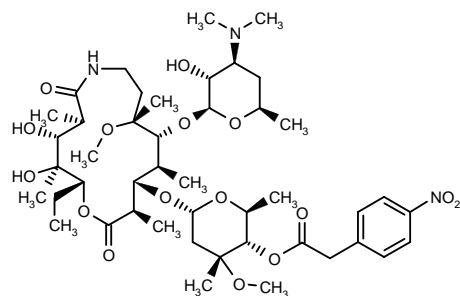
SOURCE – Abbott.

REFERENCES

1. Ma, Z. et al. (Abbott Laboratories Inc.) *6-O-Substd. erythromycin derivs. having improved gastrointestinal tolerance*. WO 0232919.

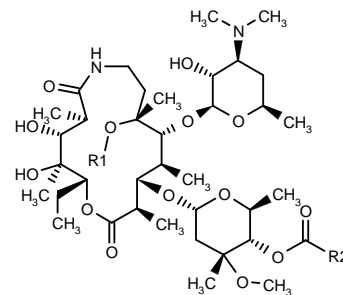
320968

6-*O*-Methyl-4''-*O*-[2-(4-nitrophenyl)acetyl]-8a-aza-8a-homoerythromycin A



C₄₅ H₇₃ N₃ O₁₆; Mol wt: 912.0767

ACTION – Erythromycin A derivative for use in the treatment of systemic and topical bacterial infections. It gave MIC values of < 0.01 and < 2 µg/ml, respectively, against erythromycin-susceptible and -resistant *Strep*-



Compound	R1	R2	Formula
320969	Me	3-quinoliny-CH=CH	C ₄₉ H ₇₅ N ₃ O ₁₄
320970	H	3-quinoliny-CH=CH	C ₄₈ H ₇₃ N ₃ O ₁₄
320971	Me	3-quinoliny-(CH ₂) ₃	C ₅₀ H ₇₉ N ₃ O ₁₄
320972	Me	1,2,3,4-tetrahydro-3-quinoliny-CH ₂ CH ₂	C ₄₉ H ₈₁ N ₃ O ₁₄

SOURCES – GlaxoSmithKline; Pliva.

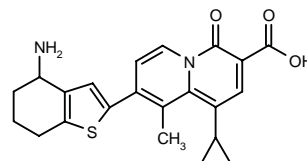
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1. Alihodzic, S. et al. (GlaxoSmithKline plc;Pliva dd) *Macrolides*. WO 0232917.

ANTIBACTERIAL DRUGS

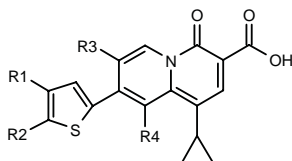
320190

8-(4-Amino-4,5,6,7-tetrahydro-1-benzothien-2-yl)-1-cyclopropyl-9-methyl-4-oxo-4*H*-quinolizine-3-carboxylic acid



C₂₂ H₂₂ N₂ O₃ S; Mol wt: 394.4928

ACTION – Antibacterial agent giving MIC values < 0.008 µg/ml against *Staphylococcus aureus* 209P. Other exemplified quinolizine derivatives include the following:



Compound	R1,R2	R3	R4	Isomer	Formula
320191	-CH(NH2)CH2CH2CH2-	F	Me		C ₂₂ H ₂₁ FN ₂ O ₃ S
320192	-CH(NH2)CH2NHC(Me)2-	F	Me		C ₂₃ H ₂₄ FN ₃ O ₃ S
320195	-CH(NH2)CH2CH2CH2-	H	Cl		C ₂₁ H ₁₉ ClN ₂ O ₃ S
320196	-CH(NH2)CH2OCH2-	H	Me		C ₂₁ H ₂₀ N ₂ O ₄ S
320197	-CH(NH2)CH2CH2CH2-	H	Me	(+)	C ₂₂ H ₂₂ N ₂ O ₃ S
320198	-CH(NH2)CH2CH2CH2-	H	Me	(-)	C ₂₂ H ₂₂ N ₂ O ₃ S
320199	-CH(cyclopropyl-NH)CH2CH2CH2-	H	Me		C ₂₅ H ₂₆ N ₂ O ₃ S
320200	-CH(OH)CH2CH2CH2-	H	Me		C ₂₂ H ₂₁ NO ₄ S
320201	-CH(NH2)CH2CH2-	H	Me		C ₂₁ H ₂₀ N ₂ O ₃ S

SOURCES – Sankyo; Ube.

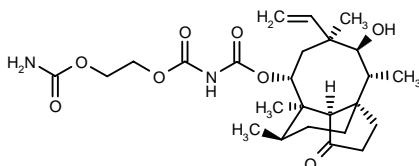
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1. Ohya, S. et al. (Sankyo Co., Ltd.;Ube Industries, Ltd.) *Quinolizine derivs.* WO 0222614.

320442

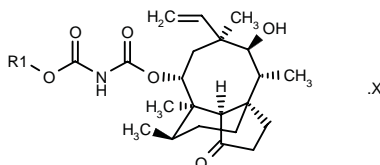
Iminodicarboxylic acid 2-(carbamoyloxy)ethyl (3a*S*,4*R*,5*S*,6*S*,8*R*,9*R*,9a*R*,10*R*)-5-hydroxy-4,6,9,10-tetramethyl-1-oxo-6-vinylperhydro-3a,9-propanocyclopentacycloocten-8-yl diester

14-*O*-[*N*-(2-Carbamoyloxyethoxycarbonyl)carbamoyl]-mutilin



C₂₅ H₃₈ N₂ O₈; Mol wt: 494.5812

ACTION – Pleuromutilin derivative with antibacterial activity, reported to be active against Gram-positive and Gram-negative bacteria including multidrug-resistant organisms. Other specifically claimed compounds are:



Compound	R1	X	Formula
320443	(<i>S</i>)-2-oxo-3-pyrrolidinyl		C ₂₆ H ₃₈ N ₂ O ₇
320444	1-azetidiny	HCl	C ₂₅ H ₃₈ N ₂ O ₆ ·HCl
320445	(<i>R</i>)-3-pyrrolidinyl		C ₂₆ H ₄₀ N ₂ O ₆
320446	(<i>S</i>)-3-pyrrolidinyl		C ₂₆ H ₄₀ N ₂ O ₆
320447	CH2CH(OH)CH2N(Me)2		C ₂₇ H ₄₄ N ₂ O ₇
320448	1-[N(Me)2CH2]-cyclopropyl		C ₂₈ H ₄₄ N ₂ O ₆

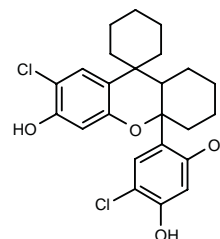
SOURCE – GlaxoSmithKline.

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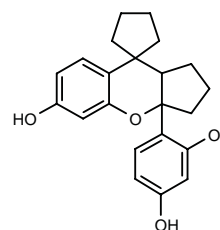
320520

4-Chloro-6-(7'-chloro-6'-hydroxy-2',3',4',4'a,5',6',9',9a'-octahydro-1'*H*-spiro[cyclohexane-1,9'-xanthen]-4a'-yl)-1,3-benzenediol



C₂₄ H₂₆ Cl₂ O₄; Mol wt: 449.3714

ACTION – Antibacterial agent with an MIC of 1.6 µM against *Staphylococcus aureus* 8325-4 and of 3.2 µM against *Escherichia coli* M31 and a panel of methicillin-resistant *S. aureus* strains. Another exemplified flavan compound is:



320521: C₂₂ H₂₄ O₄

SOURCE – RiboTargets.

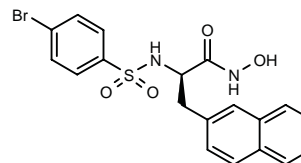
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BB-78484

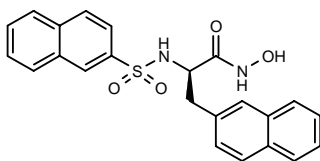
321137

*N*²-(4-Bromophenylsulfonyl)-*N*¹-hydroxy-3-(2-naphthyl)-D-alaninamide



C₁₉ H₁₇ Br N₂ O₄ S; Mol wt: 449.3233

ACTION – Antibacterial agent, an inhibitor of UDP-3-*O*-(*R*-3-hydroxymyristoyl)-*N*-acetylglucosamine deacetylase (LpxC; IC₅₀ = 400 nM) with antibacterial activity against a range of Gram-negative pathogens including *Escherichia coli*, *Morganella morganii*, *Serratia marcescens*, *Klebsiella pneumoniae* and *Burkholderia cepacia* (MIC = 1-16 µg/ml). It also exhibited bactericidal against *E. coli*. Another related compound is:



BB-78485 [321138]: C₂₃ H₂₀ N₂ O₄ S

SOURCE – British Biotech.

REFERENCES

1. Clements, J.M. et al. *Antibacterial activities and characterization of novel inhibitors of LpxC*. Antimicrob Agents Chemother 2002, 46(6): 1793.

NOVISPIRIN G10

320705

L-Lysyl-L-asparaginy-L-leucyl-L-arginyl-L-arginyl-L-isoleucyl-L-isoleucyl-L-arginyl-L-lysyl-glycyl-L-isoleucyl-L-histidyl-L-isoleucyl-L-isoleucyl-L-lysyl-L-lysyl-L-tyrosyl-glycine

C₁₀₁ H₁₈₀ N₃₄ O₂₁; Mol wt: 2206.7500

ACTION – Antimicrobial peptide with potential for the treatment of burn and other wound infections. The peptide was active against multidrug-resistant microorganisms isolated from burn patients including *Pseudomonas aeruginosa* (MIC = 0.7-1.2 µg/ml), *Staphylococcus aureus* (MIC = 4.2 µg/ml) and *Staphylococcus epidermidis* (MIC = 2.8 µg/ml). Its activity compared favorably with other antibiotics and antimicrobial peptides including protegrin-1. Compound showed rapid bactericidal activity and appeared to alter membrane permeability in *P. aeruginosa*; it was nonhemolytic and exhibited relatively low cytotoxic activity (IC₅₀ = 163 µg/ml in cervical epithelial ME-180 cells). In rats with burns infected by multidrug-resistant *P. aeruginosa*, single i.d. doses of 1, 3 or 6 mg/kg significantly and rapidly reduced bacterial counts.

SOURCES – University of California, Los Angeles, CA (US); University of Iowa, Iowa City, IA (US); University of Michigan, Ann Arbor, MI (US); Ruhr-Universität Bochum, Bochum (DE).

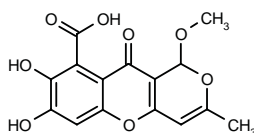
REFERENCES

1. Lehrer, R.I. et al. (University of California, Oakland; University of Iowa) *Statement as to federally sponsored research*. WO 0200839.
2. Steintraesser, L. et al. *Activity of novispirin G10 against Pseudomonas aeruginosa in vitro and in infected burns*. Antimicrob Agents Chemother 2002, 46(6): 1837.

SB-238569

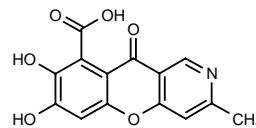
320719

7,8-Dihydroxy-1-methoxy-3-methyl-10-oxo-1H,10H-pyrano[4,3-b][1]benzopyran-9-carboxylic acid

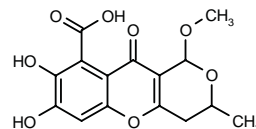


C₁₅ H₁₂ O₈; Mol wt: 320.2518

ACTION – Metallo-β-lactamase inhibitor extracted from *Chaetomium funicola*, with respective K_i values of 79, 17 and 3.4 µM against *Bacillus cereus* II, *Pseudomonas aeruginosa* IMP-1 and *Bacteroides fragilis* CfiA enzymes. Compound was inactive against angiotensin-converting enzyme (ACE) and serine β-lactamases. It showed good synergistic antibacterial activity in combination with meropenem against *B. fragilis* strains; no synergy was seen against *P. aeruginosa* or *Stenotrophomonas maltophilia*. Other related compounds are:



SB-236049 [320715]: C₁₄ H₉ N O₆



SB-236050 [320716]: C₁₅ H₁₄ O₈

SOURCE – GlaxoSmithKline.

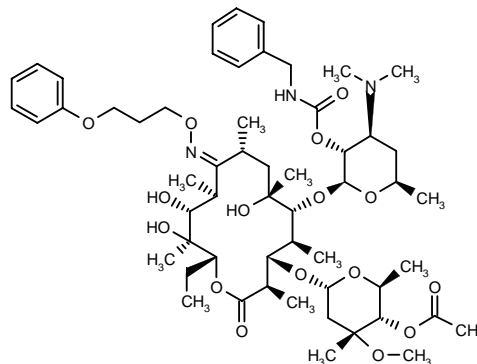
REFERENCES

1. Elson, S.W. et al. (GlaxoSmithKline SA) *Benzopyranone derivs. produced by microorganisms, process for their preparation and use as metallo-β-lactamase inhibitors*. ES 2143916.
2. Payne, D.J. et al. *Identification of a series of tricyclic natural products as potent broad-spectrum inhibitors of metallo-β-lactamases*. Antimicrob Agents Chemother 2002, 46(6): 1880.

ANTIMYCOBACTERIAL AGENTS

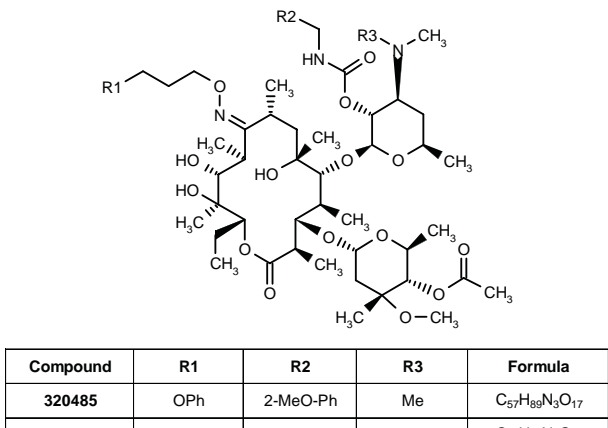
320484

4''-O-Acetyl-2'-O-(N-benzylcarbamoyl)erythromycin A 9-[O-(3-phenoxypropyl)oxime]



C₅₆ H₈₇ N₃ O₁₆; Mol wt: 1058.3080

ACTION – Antibacterial macrolide displaying MIC values of 0.10 µg/ml against *Mycobacterium avium* strains 20034, 20092 and 20096, and of 0.2 µg/ml against *M. avium* 20045 and *Mycobacterium intracellulare* strains 20066, 20067, 20073 and 20075. Other exemplified erythromycin A derivatives are:



SOURCE – Hokuriku.

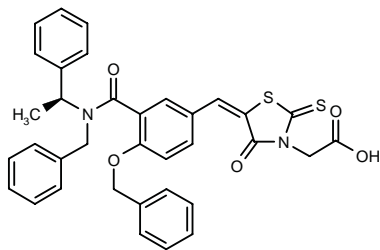
REFERENCES

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ANTIFUNGAL AGENTS

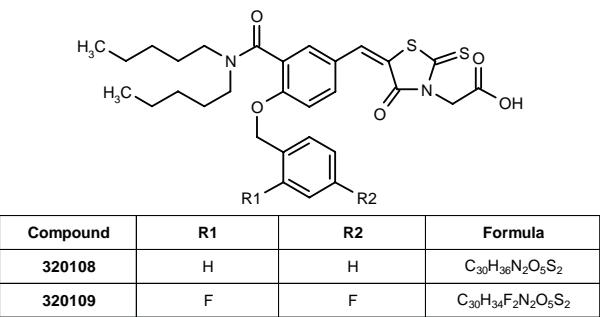
320107

2-[5-[4-(Benzyloxy)-3-[*N*-benzyl-*N*-[1(*S*)-phenylethyl]carbamoyl]benzylidene]-4-oxo-2-thioxothiazolidin-3-yl]acetic acid



C35 H30 N2 O5 S2; Mol wt: 622.7630

ACTION – Antifungal agent particularly useful for the treatment of infections caused by *Candida*, *Trichophyton*, *Microsporum*, *Cryptococcus neoformans*, *Aspergillus flavus*, *Aspergillus fumigatus*, *Coccidioides*, *Paracoccidioides*, *Histoplasma*, *Blastomyces* and *Epidermophyton*. It inhibited *Candida albicans* PMT-1 enzyme with an IC₅₀ of 0.6 μM and was shown to sensitize *C. albicans* SC5314 strain to geneticin (IC₅₀ = 0.65 μM). Other exemplified thiazolidine derivatives are:



SOURCE – Oxford GlycoSciences.

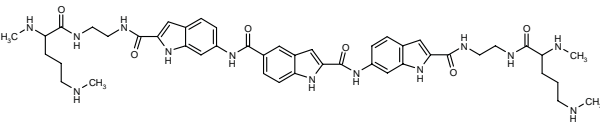
REFERENCES

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GL-406349

321010

N,N'-Bis[2-[*N*-[2-(*N*²,*N*⁵-dimethyl-DL-lysylamino)-ethyl]carbamoyl]-1*H*-indol-6-yl]-1*H*-indole-2,5-dicarboxamide



C46 H59 N13 O6; Mol wt: 890.0571

ACTION – Antifungal agent, a minor groove-binding DNA-targeting compound with broad-spectrum activity against a panel of pathogenic yeast and fungi including *Candida albicans* and *Aspergillus fumigatus* (MIC = 2.8 and 50 μM, respectively). It exhibited a favorable pharmacokinetic profile in mice after i.p. administration and increased survival in a murine model of systemic *C. albicans* infection at a dose of 10 mg/kg i.p.

SOURCE – Genelabs.

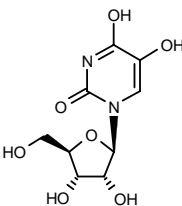
REFERENCES

1. Roberts, C. et al. *Discovery of a new class of broad-spectrum antifungal compounds that target the minor groove of DNA*. 28th Natl Med Chem Symp (June 8-12, San Diego) 2002, Abst 67.

ANTIVIRAL DRUGS

320651

5-Hydroxyuridine



C9 H12 N2 O7; Mol wt: 260.2008

ACTION – Modified nucleoside for use in the treatment of infections caused by Flaviviridae, Orthomyxoviridae or Paramyxoviridae, and also in the treatment of cancer. It was shown to prevent the infection of MDBK cells by bovine viral diarrhea virus (BVDV) at a concentration of 40 μ M.

SOURCE – Pharmasset.

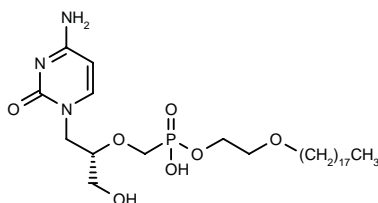
REFERENCES

1. Stuyver, L. and Watanabe, K.A. (Pharmasset, Inc.) *Modified nucleosides for treatment of viral infections and abnormal cellular proliferation*. WO 0232920.

ODE-CDV

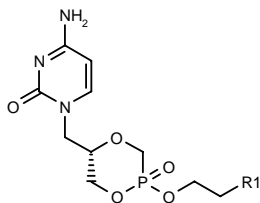
319391

2-(4-Amino-2-oxo-1,2-dihydropyrimidin-1-yl)-1-(S)-(hydroxymethyl)ethoxymethylphosphonic acid 2-(octadecyloxy)ethyl monoester



C₂₈ H₅₄ N₃ O₇ P; Mol wt: 575.7226

ACTION – Antiviral agent, a cidofovir derivative with improved efficacy against vaccinia virus (IC₅₀ = 0.2 and 46.2 μ M, respectively) and cowpox virus (IC₅₀ = 0.3 and 44.7 μ M, respectively) and an improved selectivity index compared to the parent compound. Other related compounds are:



Compound	R1	Formula
ODE-cCDV [319389]	OC18H37	C ₂₈ H ₅₂ N ₃ O ₆ P
HDP-cCDV [319390]	CH2OC16H33	C ₂₇ H ₅₀ N ₃ O ₆ P

SOURCES – University of Alabama at Birmingham, Birmingham, AL (US); University of California, San Diego, La Jolla, CA (US) Veterans Administration Medical Center, Hartford, VT (US).

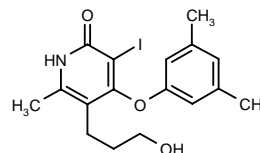
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1. Hostettler, K.Y. et al. (University of California, San Diego) *Phosphonate cpds*. WO 0139724.
2. Kern, E.R. et al. *Enhanced inhibition of orthopoxvirus replication in vitro by alkoxyalkyl esters of cidofovir and cyclic cidofovir*. Antimicrob Agents Chemother 2002, 46(4): 991.

AIDS MEDICINES

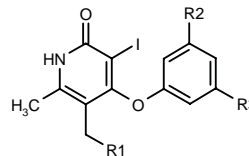
319643

4-(3,5-Dimethylphenoxy)-5-(3-hydroxypropyl)-3-iodo-6-methylpyridin-2(1H)-one



C₁₇ H₂₀ I N O₃; Mol wt: 413.2490

ACTION – Anti-HIV agent proven to inhibit the replication of HIV-1 in MT-4 cells with an IC₅₀ of 0.0006 μ M compared to a CC₅₀ for cytotoxicity of 100 μ M, yielding a selectivity index of > 150,000. Other exemplified compounds include the following:



Compound	R1	R2=R3	Formula
319644	2-Me-4-thiazolyl-CH2S	Me	C ₂₀ H ₂₁ N ₂ O ₂ S ₂
319645	Me	C(Me)=CHCN	C ₂₂ H ₂₀ N ₃ O ₂

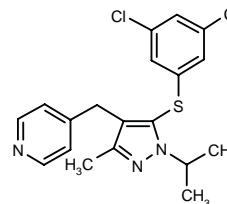
SOURCES – CNRS; Institut Curie, Paris (FR); Janssen.

REFERENCES

1. Guillemont, J. et al. (Janssen Pharmaceutica NV;CNRS [Centre National de la Recherche Scientifique];Institut Curie) *Pyridinone and pyridinethione derivs. having HIV inhibiting properties*. EP 1188748, WO 0224650.

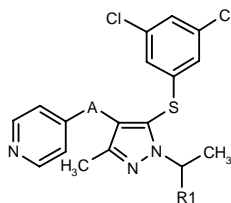
320245

4-[5-(3,5-Dichlorophenylsulfanyl)-1-isopropyl-3-methyl-1H-pyrazol-4-ylmethyl]pyridine



C₁₉ H₁₉ Cl₂ N₃ S; Mol wt: 392.3521

ACTION – HIV reverse transcriptase inhibitor (IC₅₀ = 76 nM) shown to protect MT-4 cells from HIV-induced death with an IC₅₀ of 2.7 nM. Other exemplified pyrazole derivatives are:



Compound	R1	A	Formula
320247	H	-CH2-	C ₁₈ H ₁₇ Cl ₂ N ₃ S
320248	Me	-CH2OCH2-	C ₂₀ H ₂₁ Cl ₂ N ₃ OS

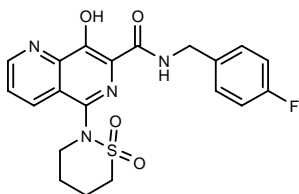
SOURCE – Roche.

REFERENCES

1. Dymock, B.W. et al. (F. Hoffmann-La Roche AG) *Pyrazole derivs. for the treatment of viral diseases*. WO 0230907.

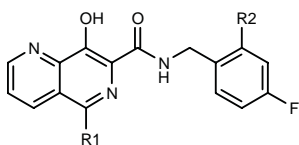
320387

5-(1,1-Dioxoperhydro-1,2-thiazin-2-yl)-N-(4-fluorobenzyl)-8-hydroxy-1,6-naphthyridine-7-carboxamide



C₂₀H₁₉F N₄ O₄ S; Mol wt: 430.4581

ACTION – HIV integrase inhibitor with potential in the treatment of HIV infection. Compounds within the scope of the invention are reported to inhibit acute HIV infection in T-lymphoid cells. Other specifically claimed naphthalenyl carboxamide derivatives are:



Compound	R1	R2	Formula
320388	N(Me)COCON(Me)2	H	C ₂₁ H ₂₀ FN ₅ O ₄
320391	1,1-dioxo-perhydro-1,2,5-thiadiazepin-2-yl	H	C ₂₀ H ₂₀ FN ₅ O ₄ S
320393	1,1-dioxo-perhydro-1,2-thiazin-2-yl	SO2Me	C ₂₁ H ₂₁ FN ₄ O ₆ S ₂

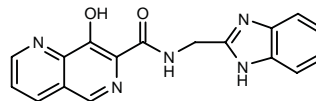
SOURCE – Merck & Co.

REFERENCES

1. Anthony, N.J. et al. (Merck & Co., Inc.) *Aza- and polyaza-naphthalenyl carboxamides useful as HIV integrase inhibitors*. WO 0230930, WO 0230931.

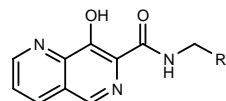
320399

N-(1H-Benzimidazol-2-ylmethyl)-8-hydroxy-1,6-naphthyridine-7-carboxamide



C₁₇H₁₃N₅O₂; Mol wt: 319.3227

ACTION – HIV integrase inhibitor with potential in the treatment of HIV infection. Compounds within the scope of the invention are reported to inhibit acute HIV infection in T-lymphoid cells. Other specifically claimed naphthalenyl carboxamide derivatives are:



Compound	R1	Formula
320402	3-indolyl-CH2	C ₁₉ H ₁₆ N ₄ O ₂
320403	2-[3,4-(MeO)2-Ph]-3-indolyl-CH2	C ₂₇ H ₂₄ N ₄ O ₄
320404	2-oxo-2,3-dihydro-1H-indol-3-yl	C ₁₈ H ₁₄ N ₄ O ₃
320405	10H-phenothiazin-10-yl-CH2	C ₂₃ H ₁₈ N ₄ O ₂ S
320406	1-Ph-2-Me-3-indolyl-CH2	C ₂₆ H ₂₂ N ₄ O ₂
320407	6-indolyl	C ₁₈ H ₁₄ N ₄ O ₂
320408	2-indolyl	C ₁₈ H ₁₄ N ₄ O ₂
320409	4-oxo-3,4-dihydro-1-phthalazinyl	C ₁₈ H ₁₃ N ₅ O ₃
320410	1-(t-BuOCO)-3-indolyl	C ₂₃ H ₂₂ N ₄ O ₄
320411	3-indolyl	C ₁₈ H ₁₄ N ₄ O ₂
320413	2,3-dihydro-imidazo[2,1-b]thiazol-6-yl	C ₁₅ H ₁₃ N ₅ O ₂ S
320414	4-Pyr	C ₁₅ H ₁₂ N ₄ O ₂
320416	2-Pyr	C ₁₅ H ₁₂ N ₄ O ₂

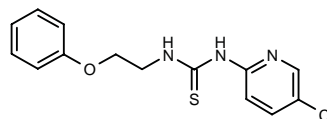
SOURCE – Merck & Co.

REFERENCES

1. Anthony, N.J. et al. (Merck & Co., Inc.) *Aza- and polyaza-naphthalenyl-carboxamides useful as HIV integrase inhibitors*. WO 0230426.

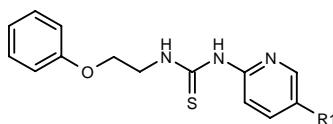
320672

1-(5-Chloropyridin-2-yl)-3-(2-phenoxyethyl)thiourea



C₁₄H₁₄Cl N₃ O S; Mol wt: 307.8036

ACTION – Anti-HIV agent, an inhibitor of HIV reverse transcriptase (IC₅₀ = 1.5 μM against recombinant enzyme) shown to inhibit the replication of the HIV strain HTLV_{IIIB} in peripheral blood mononuclear cells with an IC₅₀ value of 0.004 μM. In addition, this compound exhibited minimal cytotoxicity (CC₅₀ > 100 μM), yielding a selectivity index of > 25,000. Other exemplified compounds include the following:



Compound	R1	Formula
320673	H	C ₁₄ H ₁₅ N ₃ OS
320674	Br	C ₁₄ H ₁₄ BrN ₃ OS

SOURCE – Parker Hughes Institute, Roseville, MN (US).

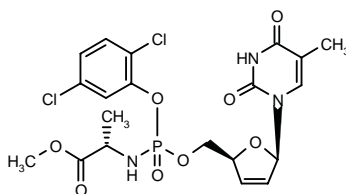
REFERENCES

1. Uckun, F.M. and Venkatachalam, T.K. (Parker Hughes Institute) *Phenoxyethyl-thiourea-pyridine cpds. and their use for the treatment of HIV-infections*. WO 0232873.

321025

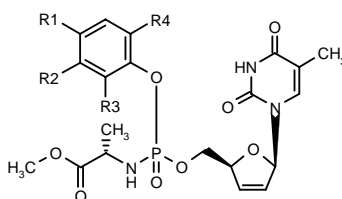
2',3'-Didehydro-3'-deoxy-5'-O-[(2,5-dichlorophenoxy)(O-methyl-L-alanino)phosphoryl]thymidine

N-[(2,5-Dichlorophenoxy)(2',3'-didehydro-3'-deoxythymidin-5'-O-yl)phosphoryl]-L-alanine methyl ester



C20 H22 Cl2 N3 O8 P; Mol wt: 534.2868

ACTION – Antiviral agent, a potent inhibitor of HIV reverse transcriptase proven to inhibit HIV replication in peripheral blood mononuclear cells with an IC₅₀ < 0.001 μM; no cytotoxicity was observed at concentrations > 100 μM. Other exemplified aryl phosphate derivatives of 2',3'-didehydro-3'-deoxythymidine are:



Compound	R1	R2	R3	R4	Formula
321027	H	N(Me)2	H	H	C ₂₂ H ₂₉ N ₄ O ₈ P
321029	H	H	OMe	OMe	C ₂₂ H ₂₈ N ₃ O ₁₀ P
321030	Br	H	H	Cl	C ₂₀ H ₂₂ BrClN ₃ O ₈ P
321031	H	H	H	Br	C ₂₀ H ₂₃ BrN ₃ O ₈ P

SOURCE – Parker Hughes Institute, Roseville, MN (US).

REFERENCES

1. Daignault, R.A. (Parker Hughes Institute) *Aryl phosphate derivs. of d4T*. WO 0238576.

2F5/2G12

316339

Combination of the human anti-HIV monoclonal antibodies 2F5 and 2G12

2F5

305362

Human MAb against the ELDKWA motif of the HIV envelope glycoprotein gp41

2G12

316338

Human MAb against a conformationally sensitive epitope in the HIV envelope glycoprotein gp120

ACTION – Combination of two human anti-HIV-1 monoclonal antibodies that recognize conserved epitopes on the envelope glycoproteins gp41 and gp120. Preclinical data demonstrated broad synergistic HIV-neutralizing effects when the antibodies were used in combination. Results of a phase I clinical trial in 7 HIV-1-infected subjects not receiving highly active antiretroviral therapy (AAART) showed that the antibodies, given as 8 separate infusions over a period of 4 weeks, were safe and well tolerated, with no clinical or laboratory abnormalities and no immunogenicity. The antibodies were not associated with a decrease in CD4 cell count, and 6 of 7 patients had a median reduction in HIV-1 RNA of 0.62 log₁₀. The antibodies exhibited long median distribution half-lives (1.02 and 2.49 days for 2F5 and 2G12, respectively), as well as long median elimination half-lives of 7-16 days.

SOURCE – Polymun.

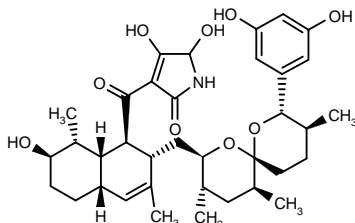
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3. Li, A. et al. *Synergistic neutralization of a chimeric SIV/HIV type 1 virus with combinations of human anti-HIV type 1 envelope monoclonal antibodies or hyperimmune globulins*. AIDS Res Hum Retroviruses 1997, 13(8): 647.
4. Li, A. et al. *Synergistic neutralization of simian-human immunodeficiency virus SHIV-vpu+ by triple and quadruple combinations of human monoclonal antibodies and high-titer anti-human immunodeficiency virus type 1 immunoglobulins*. J Virol 1998, 72(4): 3235.
5. Mascola, J.R. et al. *Potent and synergistic neutralization of human immunodeficiency virus (HIV) type 1 primary isolates by hyperimmune anti-HIV immunoglobulin combined with monoclonal antibodies 2F5 and 2G12*. J Virol 1997, 71(10): 7198.
6. Mascola, J.R. et al. *Protection of macaques against pathogenic simian/human immunodeficiency virus 89.6PD by passive transfer of neutralizing antibodies*. J Virol 1999, 73(5): 4009.
7. Mascola, J.R. et al. *Protection of macaques against vaginal transmission of a pathogenic HIV-1/SIV chimeric virus by passive infusion of neutralizing antibodies*. Nat Med 2000, 6(2): 207.
8. Verrier, F. et al. *Additive effects characterize the interaction of antibodies involved in neutralization of the primary dualtropic human immunodeficiency virus type 1 isolate 89.6*. J Virol 2001, 75(19): 9177.

INTEGRAMYCIN

320725

3-[(1*R*,2*S*,4*aR*,7*R*,8*R*,8*aR*)-2-[(2*R*,3*S*,5*S*,6*R*,8*S*,9*S*)-8-(3,5-Dihydroxyphenyl)-3,5,9-trimethyl-1,7-dioxaspiro[5.5]-undec-2-ylmethyl]-7-hydroxy-3,8-dimethyl-1,2,4*a*,5,6,7,8,8*a*-octahydronaphthalen-1-ylcarbonyl]-4,5-dihydroxy-2,5-dihydro-1*H*-pyrrol-2-one



C36 H49 N O9; Mol wt: 639.7811

ACTION – HIV-1 integrase inhibitor (IC_{50} = 4 μ M in a strand transfer assay), a natural product extracted from the fermentation of *Actinoplanes* sp.

SOURCES – Merck & Co.; Merck Sharp & Dohme.

REFERENCES

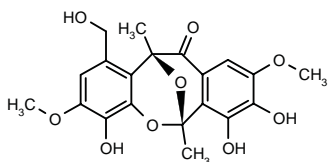
1. Heimbuch, B. et al. (Merck & Co., Inc.; Merck Sharp & Dohme Ltd.) *HIV integrase inhibitors*. US 6395743, WO 0127309.

2. Singh, S.B. et al. *Structure, stereochemistry, and biological activity of integracycin, a novel hexacyclic natural product produced by Actinoplanes sp. that inhibits HIV-1 integrase*. Org Lett 2002, 4(7): 1123.

INTEGRASTATIN A*

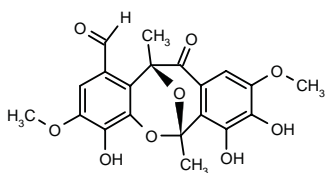
300893

(6*R**,12*R**)-4,7,8-Trihydroxy-1-(hydroxymethyl)-3,9-dimethoxy-6,12-dimethyl-11,12-dihydro-6*H*-6,12-epoxydibenzo[*b,f*]oxocin-11-one



C20 H20 O9; Mol wt: 404.3690

ACTION – Aromatic natural product extracted from fungal fermentations with potent and selective inhibitory activity against HIV-1 integrase (IC_{50} = 1.1 μ M in a strand transfer assay) and 5-10-fold selectivity over DNAase. Potentially useful for the treatment of HIV-1 infections. Another racemic tetracyclic aromatic heterocycle is:



Integrastatin B [300892]:** C20 H18 O9

SOURCES – Merck & Co.; Merck Sharp & Dohme.

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1. Dombrowski, A. et al. (Merck & Co., Inc.) *HIV integrase inhibitors*. WO 0109114.

2. Singh, S.B. et al. *Integrastatins: Structure and HIV-1 integrase inhibitory activities of two novel racemic tetracyclic aromatic heterocycles produced by two fungal species*. Tetrahedron Lett 2002, 43(13): 2351.

*Identified compound **300893** (see **300892**) Drug Data Rep 2001, 023(07): 0690.

Identified compound **300892 Drug Data Rep 2001, 023(07): 0690.

TREATMENT OF PROTOZOAL DISEASES

319394

N-Propionyl-L-alanyl-L-leucyl-L-tryptophyl-L-lysyl-L-threonyl-L-leucyl-L-leucyl-L-lysyl-L-lysyl-L-valyl-L-leucyl-L-lysyl-L-alaninamide

C77 H135 N19 O15; Mol wt: 1567.0310

ACTION – Antimalarial agent, a dermaseptin S4 derivative with time-dependent and irreversible growth-inhibitory activity against *Plasmodium falciparum*, giving IC_{50} values of 4.33 and 3.80 μ M in synchronized cultures at the ring and trophozoite stage, respectively. Unlike the parent drug, the compound affected parasite viability in a manner dissociated from lysis of host cells; the ratio between percent inhibition of parasite growth and percent hemolysis was 600 for the compound compared to 180 for the parent drug. Another related compound is:

N-Isobutyryl-L-alanyl-L-leucyl-L-tryptophyl-L-lysyl-L-threonyl-L-leucyl-L-leucyl-L-lysyl-L-lysyl-L-valyl-L-leucyl-L-lysyl-L-alaninamide

319395: C78 H137 N19 O15

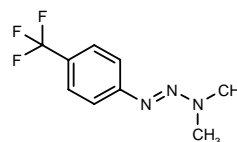
SOURCE – Hebrew University, Jerusalem (IL).

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1. Dagan, A. et al. *In vitro antiplasmodium effects of dermaseptin S4 derivatives*. Antimicrob Agents Chemother 2002, 46(4): 1059.

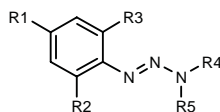
320239

3,3-Dimethyl-1-[4-(trifluoromethyl)phenyl]-1-triazene



C9 H10 F3 N3; Mol wt: 217.1930

ACTION – Antimalarial and nematocidal agent with *in vivo* antimalarial activity following s.c. administration to *Plasmodium berghei*-infected mice (2 x 100 mg/kg). Other exemplified triazene compounds are:



Compound	R1	R2	R3	R4	R5	Formula
320240	Cl	H	H	Me	Me	C ₈ H ₁₀ ClN ₃
320241	Me	Me	Me	Me	Me	C ₁₁ H ₁₇ N ₃
320243	H	Me	Me	-(CH ₂) ₄ -		C ₁₂ H ₁₇ N ₃
320244	Me	Me	Me	-(CH ₂) ₄ -		C ₁₃ H ₁₉ N ₃

SOURCE – Shionogi.

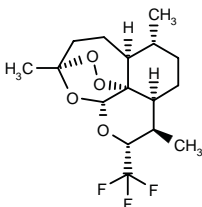
REFERENCES

1. Kawaguchi, Y. et al. (Shionogi & Co. Ltd.) *Anti-malarial agents and nematocidal agents containing triazine cpds.* JP 2002097133.

320756

(3*R*,5*aS*,6*R*,8*aS*,9*R*,10*R*,12*R*,12*aR*)-3,6,9-Trimethyl-10-(trifluoromethyl)perhydro-3,12-epoxypyran[4,3-*j*]-1,2-benzodioxepine

10-Deoxo-10(*R*)-(trifluoromethyl)artemisin



C₁₆ H₂₃ F₃ O₄; Mol wt: 336.3477

ACTION – Antimalarial agent, an artemisinin derivative with *in vitro* activity against the chloroquine-resistant *Plasmodium falciparum* W2 strain similar to that of artemether (IC₅₀ = 6.2 and 7 nM, respectively). Preliminary *in vivo* experiments showed that a dose of 35.3 μmol/kg induced good protection against *P. falciparum* infections.

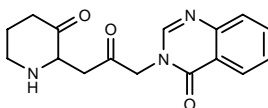
SOURCES – CNRS; CNST, Hanoi (VN).

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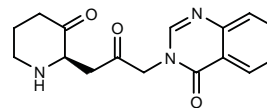
320791

(±)-3-[2-Oxo-3-(3-oxopiperidin-2-yl)propyl]quinazolin-4(3*H*)-one

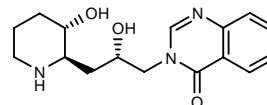


C₁₆ H₁₇ N₃ O₃; Mol wt: 299.3283

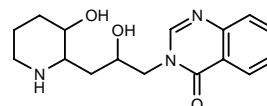
ACTION – Antimalarial agent active *in vitro* against *Plasmodium falciparum* (EC₅₀ = 20 nM), with low cytotoxicity against FM3A cells (IC₅₀ = 10 μM). *In vivo*, the racemic mixture showed antimalarial activity in mice infected with *Plasmodium berghei* (ED₅₀ = 1.3 μmol/kg i.p.) and administration of a dose of 8.9 μmol/kg/day i.p. for 4 days doubled the survival rate. Other related compounds are:



319382: C₁₆ H₁₇ N₃ O₃



320793: C₁₆ H₂₁ N₃ O₃



320796: C₁₆ H₂₁ N₃ O₃

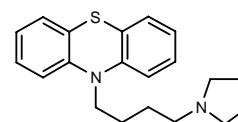
SOURCES – Nagasaki University, Nagasaki (JP); Okayama University, Okayama (JP) Tohoku University, Sendai (JP).

REFERENCES

1. Kikuchi, H. et al. *Potent antimalarial febri-fugine analogues against the Plasmodium malaria parasite.* J Med Chem 2002, 45(12): 2563.

320817

10-[4-(1-Pyrrolidinyl)butyl]-10*H*-phenothiazine



C₂₀ H₂₄ N₂ S; Mol wt: 324.4896

ACTION – Multidrug resistance modulator able to completely restore the sensitivity to chloroquine in chloroquine-resistant *Plasmodium falciparum*-infected cells at 50 ng/ml. Compound also exhibited intrinsic antimalarial activity at < 50 ng/ml. *In vivo* experiments in monkeys infected with chloroquine-resistant *P. falciparum* are in progress.

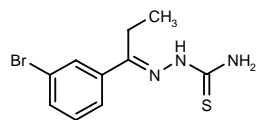
SOURCE – Walter Reed Army Institute, Washington, DC (US).

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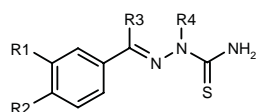
320879

1-(3-Bromophenyl)propan-1-one thiosemicarbazone



C10 H12 Br N3 S; Mol wt: 286.1958

ACTION – Antitrypanosomal agent, an inhibitor of the trypanosomal cysteine protease cruzain (IC_{50} = 100 nM) proven to prolong the survival of *Trypanosoma cruzi*-infected J774 macrophages by 42 days at 10 μ M. Other related thiosemicarbazones are:



Compound	R1	R2	R3	R4	Formula
320880	Cl	Cl	-(CH2)2-		C ₁₀ H ₈ Cl ₂ N ₃ S
320881	Cl	Cl	Me	H	C ₉ H ₉ Cl ₂ N ₃ S
320882	CF ₃	H	Et	H	C ₁₁ H ₁₂ F ₃ N ₃ S
320883	Cl	H	-CH(Me)CH2-		C ₁₁ H ₁₂ ClN ₃ S
320884	CF ₃	H	-CH(Me)CH2-		C ₁₂ H ₁₂ F ₃ N ₃ S

SOURCE – Pfizer.

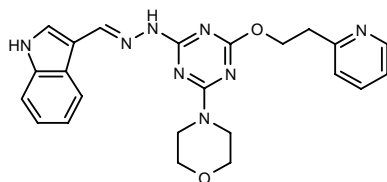
REFERENCES

1. Du, X. et al. *Synthesis and structure-activity relationship study of potent trypanocidal thio semicarbazone inhibitors of the trypanosomal cysteine protease cruzain*. J Med Chem 2002, 45(13): 2695.

TREATMENT OF SEPTIC SHOCK

320801

1*H*-Indole-3-carbaldehyde [4-(4-morpholinyl)-6-[2-(2-pyridyl)ethoxy]-1,3,5-triazin-2-yl]hydrazone



C23 H24 N8 O2; Mol wt: 444.4966

ACTION – IL-12 production inhibitor, potentially useful for the treatment of sepsis and autoimmune disorders including rheumatoid arthritis, Crohn's disease, psoriasis and multiple sclerosis.

SOURCE – Shionogi BioResearch.

REFERENCES

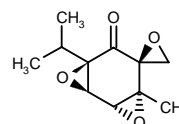
1. Ono, M. et al. (Shionogi BioResearch Corp.) *Inhibitors of IL-12 production*. US 6384032.

TREATMENT OF MUSCULOSKELETAL AND CONNECTIVE TISSUE DISEASES

ANTIARTHRITIC DRUGS

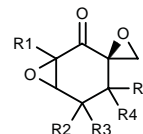
319757

(1*R*,2*R*,4*R*,5*S*,7*R*)-7-Isopropyl-4-methylspiro[3,8-dioxatricyclo[5.1.0.0^{2,4}]octane-5,2'-oxiran]-6-one



C11 H14 O4; Mol wt: 210.2276

ACTION – Triptolide analogue with the ability to induce 15-lipoxygenase (15-LO), and thus potentially useful for the treatment of autoimmune and inflammatory disorders. Other exemplified compounds are:



Compound	R1	R2	R3	R4	R5	Isomer	Formula
319758	i-Pr	H	-O-	Me	1S,2S,4S,7S		C ₁₁ H ₁₄ O ₄
319760	cyclohexyl	H	-O-	Me	1R,2R,4R,7R		C ₁₄ H ₁₈ O ₄
319762	cyclohexyl	H	-O-	Me	1S,2S,4S,7S		C ₁₄ H ₁₈ O ₄
319763	t-Bu	H	bond	Me	1S,6S		C ₁₂ H ₁₆ O ₃
319764	t-Bu	H	-O-	Me	1S,2S,4S,7S		C ₁₂ H ₁₆ O ₄
319765	t-Bu	Me	-O-	H	1R,2R,4R,7R		C ₁₂ H ₁₆ O ₄
319766	t-Bu	Me	-O-	H	1S,2S,4S,7S		C ₁₂ H ₁₆ O ₄

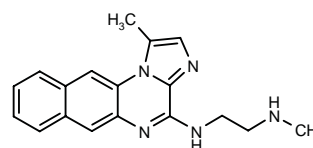
SOURCE – Emory University, Atlanta, GA (US).

REFERENCES

1. Venkatesan, H. et al. (Emory University) *Triptolide analogs for the treatment of autoimmune and inflammatory disorders*. WO 0228862.

319774

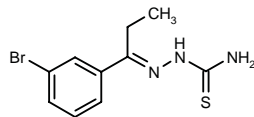
*N*¹-Methyl-*N*²-(1-methylbenzo[*g*]imidazo[1,2-*a*]quinoxalin-4-yl)ethane-1,2-diamine



C18 H19 N5; Mol wt: 305.3831

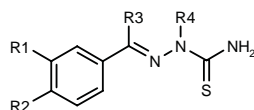
320879

1-(3-Bromophenyl)propan-1-one thiosemicarbazone



C10 H12 Br N3 S; Mol wt: 286.1958

ACTION – Antitrypanosomal agent, an inhibitor of the trypanosomal cysteine protease cruzain (IC₅₀ = 100 nM) proven to prolong the survival of *Trypanosoma cruzi*-infected J774 macrophages by 42 days at 10 µM. Other related thiosemicarbazones are:



Compound	R1	R2	R3	R4	Formula
320880	Cl	Cl	-(CH2)2-		C ₁₀ H ₉ Cl ₂ N ₃ S
320881	Cl	Cl	Me	H	C ₉ H ₉ Cl ₂ N ₃ S
320882	CF ₃	H	Et	H	C ₁₁ H ₁₂ F ₃ N ₃ S
320883	Cl	H	-CH(Me)CH2-		C ₁₁ H ₁₂ ClN ₃ S
320884	CF ₃	H	-CH(Me)CH2-		C ₁₂ H ₁₂ F ₃ N ₃ S

SOURCE – Pfizer.

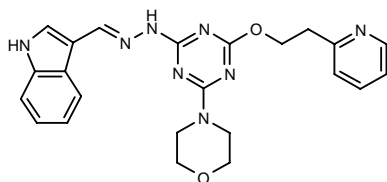
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TREATMENT OF SEPTIC SHOCK

320801

1*H*-Indole-3-carbaldehyde [4-(4-morpholinyl)-6-[2-(2-pyridyl)ethoxy]-1,3,5-triazin-2-yl]hydrazone



C23 H24 N8 O2; Mol wt: 444.4966

ACTION – IL-12 production inhibitor, potentially useful for the treatment of sepsis and autoimmune disorders including rheumatoid arthritis, Crohn's disease, psoriasis and multiple sclerosis.

SOURCE – Shionogi BioResearch.

REFERENCES

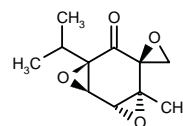
1. Ono, M. et al. (Shionogi BioResearch Corp.) *Inhibitors of IL-12 production*. US 6384032.

TREATMENT OF MUSCULOSKELETAL AND CONNECTIVE TISSUE DISEASES

ANTIARTHRITIC DRUGS

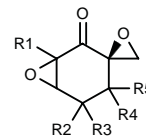
319757

(1*R*,2*R*,4*R*,5*S*,7*R*)-7-Isopropyl-4-methylspiro[3,8-dioxatricyclo[5.1.0.0^{2,4}]octane-5,2'-oxiran]-6-one



C11 H14 O4; Mol wt: 210.2276

ACTION – Triptolide analogue with the ability to induce 15-lipoxygenase (15-LO), and thus potentially useful for the treatment of autoimmune and inflammatory disorders. Other exemplified compounds are:



Compound	R1	R2	R3	R4	R5	Isomer	Formula
319758	i-Pr	H	-O-	Me	1 <i>S</i> ,2 <i>S</i> ,4 <i>S</i> ,7 <i>S</i>		C ₁₁ H ₁₄ O ₄
319760	cyclohexyl	H	-O-	Me	1 <i>R</i> ,2 <i>R</i> ,4 <i>R</i> ,7 <i>R</i>		C ₁₄ H ₁₈ O ₄
319762	cyclohexyl	H	-O-	Me	1 <i>S</i> ,2 <i>S</i> ,4 <i>S</i> ,7 <i>S</i>		C ₁₄ H ₁₈ O ₄
319763	t-Bu	H	bond	Me	1 <i>S</i> ,6 <i>S</i>		C ₁₂ H ₁₆ O ₃
319764	t-Bu	H	-O-	Me	1 <i>S</i> ,2 <i>S</i> ,4 <i>S</i> ,7 <i>S</i>		C ₁₂ H ₁₆ O ₄
319765	t-Bu	Me	-O-	H	1 <i>R</i> ,2 <i>R</i> ,4 <i>R</i> ,7 <i>R</i>		C ₁₂ H ₁₆ O ₄
319766	t-Bu	Me	-O-	H	1 <i>S</i> ,2 <i>S</i> ,4 <i>S</i> ,7 <i>S</i>		C ₁₂ H ₁₆ O ₄

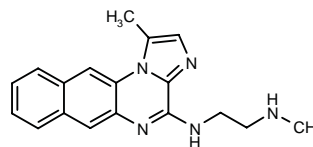
SOURCE – Emory University, Atlanta, GA (US).

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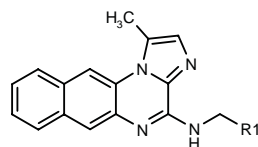
319774

*N*¹-Methyl-*N*²-(1-methylbenzo[*g*]imidazo[1,2-*a*]quinoxalin-4-yl)ethane-1,2-diamine

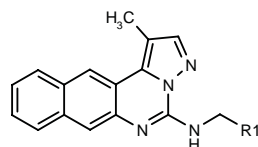


C18 H19 N5; Mol wt: 305.3831

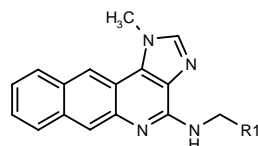
ACTION – Antiinflammatory agent reported to be useful for the treatment of disorders mediated by NF- κ B and/or TNF- α , particularly rheumatoid arthritis, asthma, inflammatory bowel disease, chronic obstructive pulmonary disease and psoriasis, as well as HIV and HSV-1 infection, breast cancer, prostate cancer and Hodgkin's lymphoma. Other specifically claimed tetracyclic compounds are:



Compound	R1	Formula
319777	H	C ₁₆ H ₁₄ N ₄
319784	CH ₂ OH	C ₁₇ H ₁₆ N ₄ O
319786	1-Pip-CH ₂	C ₂₂ H ₂₆ N ₅



Compound	R1	Formula
319779	CH ₂ NHMe	C ₁₈ H ₁₉ N ₅
319780	H	C ₁₆ H ₁₄ N ₄



Compound	R1	Formula
319782	H	C ₁₆ H ₁₄ N ₄
319783	CH ₂ NHMe	C ₁₈ H ₁₉ N ₅

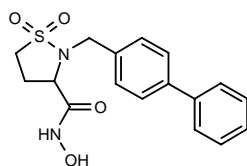
SOURCE – Bristol-Myers Squibb.

REFERENCES

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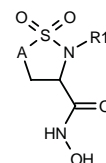
319858

2-(Biphenyl-4-ylmethyl)-1,1-dioxisothiazolidine-3-carboxyhydroxamic acid

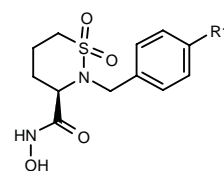


C₁₇ H₁₈ N₂ O₄ S; Mol wt: 346.4052

ACTION – Matrix metalloproteinase inhibitor, potentially useful for the treatment of inflammatory diseases, as well as infections, age-related macular degeneration, alcoholism, allergy, asthma, atherosclerosis, atopic dermatitis, autoimmune diseases, cachexia, chronic obstructive pulmonary disease, congestive heart failure, Crohn's disease, fever, fibromyalgia, gout, transplant rejection, multiple sclerosis, cancer, etc. Other specifically claimed sulfur-containing cyclic compounds are:



Compound	R1	A	Formula
319861	4-(4-MeO-PhO)-PhCH ₂	CH ₂	C ₁₈ H ₂₀ N ₂ O ₆ S
319869	4-(2-Me-4-quinolinyl-CH ₂ O)-PhCH ₂	CH ₂	C ₂₂ H ₂₃ N ₃ O ₅ S
319870	4-(2-Me-4-quinolinyl-CH ₂ O)-Ph	NH	C ₂₀ H ₂₀ N ₄ O ₅ S



Compound	R1	Formula
319862	3,4-(MeO) ₂ -Ph	C ₂₀ H ₂₄ N ₂ O ₆ S
319863	4-t-Bu-Ph	C ₂₂ H ₂₈ N ₂ O ₄ S
319864	3,4-(Cl) ₂ -Ph	C ₁₈ H ₁₆ Cl ₂ N ₂ O ₄ S
319866	5-Cl-2-thienyl	C ₁₆ H ₁₇ ClN ₂ O ₄ S ₂
319868	3-Pyr	C ₁₇ H ₁₉ N ₃ O ₄ S

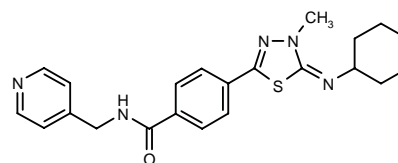
SOURCE – Bristol-Myers Squibb.

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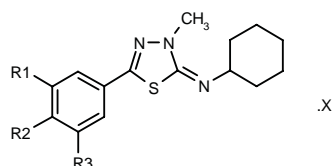
319888

4-[5-(Cyclohexylimino)-4-methyl-4,5-dihydro-1,3,4-thiadiazol-2-yl]-N-(pyridin-4-ylmethyl)benzamide

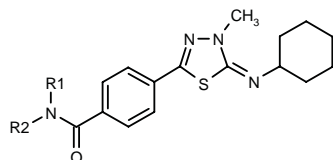


C₂₂ H₂₅ N₅ O S; Mol wt: 407.5395

ACTION – Phosphodiesterase type 7 (PDE7) inhibitor (IC₅₀ = 0.044 μ M) with potential in the treatment of a broad range of T-cell-related diseases including visceral pain, inflammatory bowel disease, osteoarthritis, multiple sclerosis, chronic obstructive pulmonary disease, asthma, cancer, AIDS and transplant rejection. Other exemplified compounds are:



Compound	R1	R2	R3	X	Formula
319889	OH	OMe	OH	CF ₃ SO ₃ H	C ₁₆ H ₂₁ N ₃ O ₃ S·CHF ₃ O ₃ S
319890	OMe	OMe	OH	CF ₃ SO ₃ H	C ₁₇ H ₂₃ N ₃ O ₃ S·CHF ₃ O ₃ S
319891	SO ₂ NH ₂	Cl	H		C ₁₈ H ₁₉ ClN ₄ O ₂ S ₂



Compound	R1	R2	Formula
319892	H	H	C ₁₆ H ₂₀ N ₄ OS
319893	H	8-quinolyl	C ₂₅ H ₂₅ N ₅ OS
319894	H	2,6-(MeO)2-3-Pyr	C ₂₃ H ₂₇ N ₅ O ₃ S
319895	H	i-Pr	C ₁₉ H ₂₆ N ₄ OS
319896	H	Et	C ₁₈ H ₂₄ N ₄ OS
319897	H	CH ₂ CH ₂ N(Me) ₂	C ₂₀ H ₂₉ N ₅ OS
319898	Me	1-Me-4-Pip	C ₂₃ H ₃₃ N ₅ OS

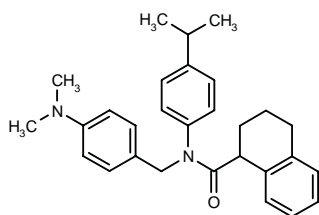
SOURCE – Pfizer.

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1. Vergne, F. et al. (Pfizer Inc.) *New thiadiazoles and oxadiazoles and their use as phosphodiesterase-7 inhibitors*. EP 1193261, WO 0228847.

319955

N-[4-(Dimethylamino)benzyl]-*N*-(4-isopropylphenyl)-1,2,3,4-tetrahydronaphthalene-1-carboxamide



C₂₉ H₃₄ N₂ O; Mol wt: 426.6006

ACTION – A representative compound from a series of amide derivatives that act as C5a receptor antagonists. It gave an IC₅₀ of 104 nM at C5a receptors in U-937 cells, and was able to inhibit C5a-stimulated calcium influx, reactive oxygen species production and cell migration in human neutrophils with IC₅₀ values of 5, 10 and 100 nM, respectively. Potentially useful for the treatment of inflammatory disorders including rheumatoid arthritis, systemic lupus erythematosus, sepsis, adult respiratory distress syndrome, chronic obstructive pulmonary disease, asthma, atherosclerosis, myocardial and cerebral infarction, psoriasis, Alzheimer's disease and bacterial and viral infections.

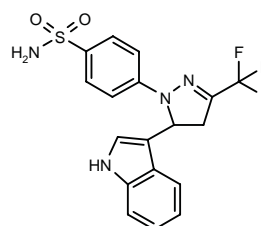
SOURCE – Mitsubishi Pharma.

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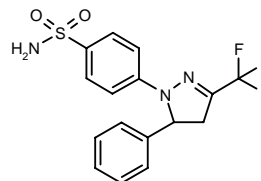
320238

4-[5-(1*H*-Indol-3-yl)-3-(trifluoromethyl)-4,5-dihydro-1*H*-pyrazol-1-yl]benzenesulfonamide



C₁₈ H₁₅ F₃ N₄ O₂ S; Mol wt: 408.4025

ACTION – Cyclooxygenase type 2 (COX-2) inhibitor (IC₅₀ = 0.078 μM), potentially useful for the treatment of disorders associated with inflammation, neoplasia and angiogenesis such as arthritis, pain, asthma, bronchitis, psoriasis, dermatitis, inflammatory bowel disease, Crohn's disease, irritable bowel syndrome, gastritis, type 1 diabetes, fever, cancer, diabetic retinopathy and endometriosis. Another exemplified 1-(4-sulfamoylphenyl)-pyrazole derivative is:



320242: C₁₆ H₁₄ F₃ N₃ O₂ S

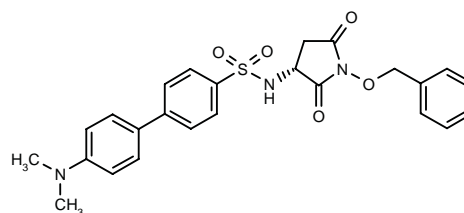
SOURCE – Temple University, Philadelphia, PA (US).

REFERENCES

1. Reddy, E.P. and Reddy, M.R. (Temple University) *1-(4-Sulfamoylphenyl)-3-substd.-5-aryl-2-pyrazolines and inhibitors of cyclooxygenase-2*. US 6376519.

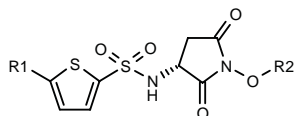
320315

N-[1-(Benzyloxy)-2,5-dioxopyrrolidin-3(*R*)-yl]-4'-(dimethylamino)biphenyl-4-sulfonamide

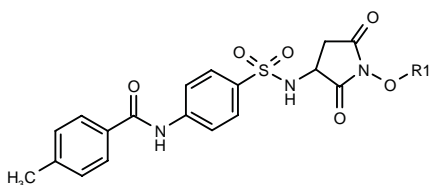


C₂₅ H₂₅ N₃ O₅ S; Mol wt: 479.5545

ACTION – Matrix metalloproteinase MMP-2 (gelatinase A) inhibitor ($IC_{50} = 0.00642 \mu M$), with potential in the treatment of osteoarthritis, rheumatoid arthritis, corneal ulcer, periodontitis, HIV infection, arteriosclerosis, atherosclerosis, restenosis, sepsis, coronary thrombosis, multiple sclerosis, open-angle glaucoma, retinopathy, psoriasis, diabetes, inflammation, osteoporosis, cancer, malaria, heart failure and asthma, among other MMP-2-mediated disorders. Other exemplified compounds are:



Compound	R1	R2	Formula
320317	4-Me-Ph-ethynyl	H	$C_{17}H_{14}N_2O_5S_2$
320318	2-benzothienyl	CH ₂ Ph	$C_{23}H_{18}N_2O_5S_3$
320319	2-benzothienyl	H	$C_{16}H_{12}N_2O_5S_3$
320320	2-benzothienyl	Me	$C_{17}H_{14}N_2O_5S_3$



Compound	R1	Isomer	Formula
320322	CH ₂ Ph	R	$C_{25}H_{23}N_3O_6S$
320323	H	R	$C_{18}H_{17}N_3O_6S$
320324	Me	S	$C_{19}H_{19}N_3O_6S$

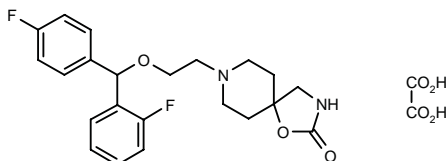
SOURCE – Shionogi.

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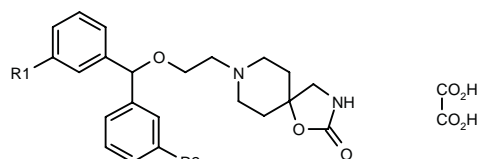
320567

8-[2-[1-(2-Fluorophenyl)-1-(4-fluorophenyl)methoxy]ethyl]-1-oxa-3,8-diazaspiro[4.5]decan-2-one oxalate



C₂₂ H₂₄ F₂ N₂ O₃ . C₂ H₂ O₄; Mol wt: 492.4724

ACTION – Agent with the ability to selectively inhibit the immune activity of Th1 cells and induce the production of IL-4 and/or IL-10 in Th2 cells; it gave an ED₃₀ value of 0.028 $\mu g/ml$ for inducing the production of IL-10 and an ED₂₀₀ value of 0.025 $\mu g/ml$ for inducing IL-4 production in murine T-cells. Potentially useful for the treatment of rheumatoid arthritis and organ-specific autoimmune diseases including diabetes, multiple sclerosis, inflammatory bowel disease, glomerulonephritis, hepatitis, allergic encephalitis, demyelinating disease, myasthenia gravis, uveitis, viral cardiomyopathy, psoriasis, etc. Other exemplified benzhydryl derivatives are:



Compound	R1	R2	Formula
320568	Me	H	$C_{23}H_{28}N_2O_3 \cdot C_2H_2O_4$
320569	CF ₃	CF ₃	$C_{24}H_{24}F_6N_2O_3 \cdot C_2H_2O_4$

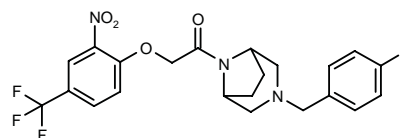
SOURCE – Sankyo.

REFERENCES

1. Shiraishi, A. et al. (Sankyo Co., Ltd.) *Benzhydryl derivs*. WO 0230938.

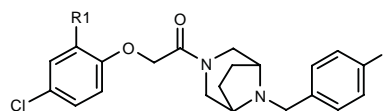
320633

1-[3-(4-Fluorobenzyl)-3,8-diazabicyclo[3.2.1]octan-8-yl]-2-[2-nitro-4-(trifluoromethyl)phenoxy]ethanone

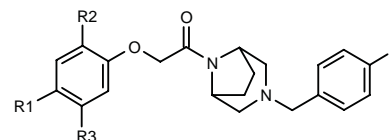


C₂₂ H₂₁ F₄ N₃ O₄; Mol wt: 467.4169

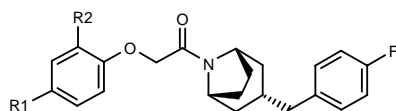
ACTION – Chemokine CCR1 receptor antagonist, potentially useful for the treatment of a broad range of inflammatory and immune disorders including rheumatoid arthritis, type 1 diabetes, lupus, inflammatory bowel diseases, optic neuritis, psoriasis, multiple sclerosis, polymyalgia rheumatica, uveitis, vasculitis, osteoarthritis, adult respiratory distress syndrome, ischemia-reperfusion injury, glomerulonephritis, chronic obstructive pulmonary disease, allergy, asthma and atopic dermatitis, among others. Other exemplified piperazine derivatives are:



Compound	R1	Formula
320634	CONH ₂	$C_{22}H_{23}ClFN_3O_3$
320637	NHCONH ₂	$C_{22}H_{24}ClFN_4O_3$



Compound	R1	R2	R3	Formula
320635	H	CO ₂ H	Cl	$C_{22}H_{22}ClFN_2O_4$
320636	Cl	5-tetrazolyl-NHCO	H	$C_{23}H_{23}ClFN_7O_3$
320638	H	NHSO ₂ Me	Cl	$C_{22}H_{25}ClFN_3O_4S$



Compound	R1	R2	Formula
320639	Cl	Ac	C ₂₄ H ₂₅ ClFNO ₃
320640	CF ₃	NHCONH ₂	C ₂₄ H ₂₅ F ₄ N ₃ O ₃
320641	Cl	NHCH ₂ CH ₂ NHSO ₂ Me	C ₂₅ H ₃₁ ClFN ₃ O ₄ S

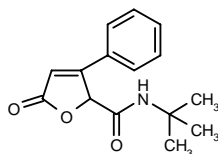
SOURCE – Pfizer.

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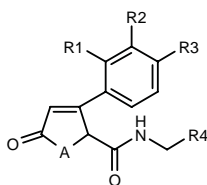
320642

N-*tert*-Butyl-5-oxo-3-phenyl-2,5-dihydrofuran-2-carboxamide

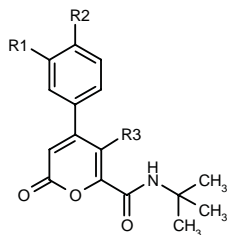


C₁₅ H₁₇ N O₃; Mol wt: 259.3033

ACTION – Protein kinase inhibitor, potentially useful for the treatment of rheumatoid arthritis, asthma, multidrug resistance, chronic obstructive pulmonary disease, acute respiratory distress syndrome, cancer, stroke, Alzheimer's disease, osteoarthritis, septic shock, angiogenesis, dermatitis and pulmonary diseases, as well as for stimulating nerve growth. Other exemplified compounds are:



Compound	R1	R2	R3	R4	A	Formula
320643	H	H	H	<i>t</i> -BuOCO	-O-	C ₁₇ H ₁₉ NO ₅
320647	-CH=CHCH=CH-	H	Ph		-O-	C ₂₂ H ₁₇ NO ₃
320648	H	H	Cl	vinyl	-O-	C ₁₄ H ₁₂ ClNO ₃
320649	H	H	OMe	CH ₂ CO-CH ₂ OMe	-N[CH ₂ CH ₂ -CH(Ph) ₂]-	C ₃₂ H ₃₄ N ₂ O ₅



Compound	R1	R2	R3	Formula
320644	H	F	H	C ₁₆ H ₁₆ FNO ₃
320645	H	H	Ph	C ₂₂ H ₂₁ NO ₃
320646	CN	H	H	C ₁₇ H ₁₆ N ₂ O ₃
320650	H	H	H	C ₁₆ H ₁₇ NO ₃

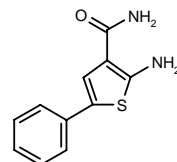
SOURCE – Morphochem.

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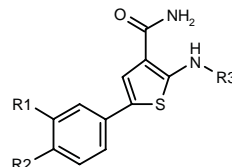
320740

2-Amino-5-phenylthiophene-3-carboxamide



C₁₁ H₁₀ N₂ O S; Mol wt: 218.2790

ACTION – An inhibitor of IκB kinase-β (IKK-β), thereby preventing the activation of NF-κB. Potentially useful for the treatment of a broad range of inflammatory and autoimmune disorders including rheumatoid arthritis, inflammatory bowel disease, asthma, chronic obstructive pulmonary disease, osteoarthritis, osteoporosis, fibrosis, psoriasis, atopic dermatitis, UV-induced skin damage, systemic lupus erythematosus, multiple sclerosis, transplant rejection, Alzheimer's disease, stroke, atherosclerosis, restenosis, diabetes, glomerulonephritis, cancer, cachexia, AIDS-related inflammation, adult respiratory distress syndrome and ataxia. Other specifically claimed compounds include the following:

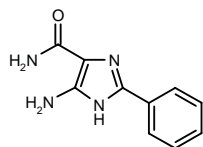


Compound	R1	R2	R3	Formula
320741	H	H	4-Pyr-CH ₂	C ₁₇ H ₁₅ N ₃ OS
320743	OMe	OMe	Ac	C ₁₈ H ₁₆ N ₂ O ₄ S
320744	H	H	CONHMe	C ₁₃ H ₁₃ N ₃ O ₂ S
320745	F	H	Ac	C ₁₃ H ₁₁ FN ₂ O ₂ S
320746	H	F	CONHMe	C ₁₃ H ₁₂ FN ₂ O ₂ S
320747	H	F	CSNHMe	C ₁₃ H ₁₂ FN ₃ OS ₂
320748	CN	H	Ac	C ₁₄ H ₁₁ N ₃ O ₂ S
320749	H	NHAc	Ac	C ₁₈ H ₁₅ N ₃ O ₃ S

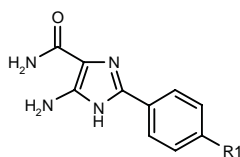
SOURCE – GlaxoSmithKline.

REFERENCES

1. Callahan, J.F. and Roshak, A.K. (GlaxoSmithKline Inc.) *NF-κB inhibitors.* WO 0230353.

3207505-Amino-2-phenyl-1*H*-imidazole-4-carboxamideC₁₀ H₁₀ N₄ O; Mol wt: 202.2160

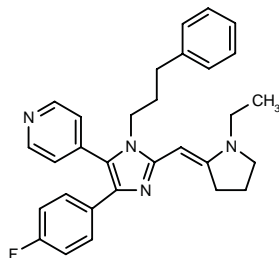
ACTION – IκB kinase-β (IKK-β) inhibitor, thereby preventing the activation of NF-κB. Potentially useful for the treatment of a broad range of inflammatory and autoimmune disorders including rheumatoid arthritis, inflammatory bowel disease, asthma, chronic obstructive pulmonary disease, osteoarthritis, osteoporosis, fibrosis, psoriasis, atopic dermatitis, UV-induced skin damage, systemic lupus erythematosus, multiple sclerosis, transplant rejection, Alzheimer's disease, stroke, atherosclerosis, restenosis, diabetes, glomerulonephritis, cancer, cachexia, AIDS-related inflammation, adult respiratory distress syndrome and ataxia. Other specifically claimed compounds include the following:



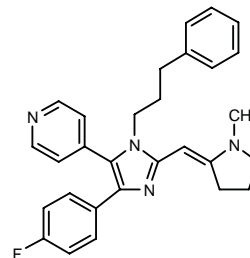
Compound	R1	Formula
320751	NO ₂	C ₁₀ H ₉ N ₅ O ₃
320752	Cl	C ₁₀ H ₉ ClN ₄ O

SOURCE – GlaxoSmithKline.**REFERENCES**

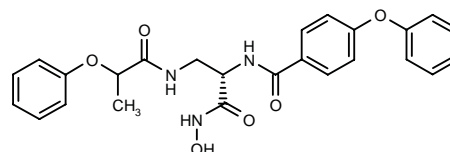
1. Callahan, J.F. and Roshak, A.K. (GlaxoSmithKline Inc.) *NF-κB inhibitors*. WO 0230423.

3207884-[2-(1-Ethylpyrrolidin-2-ylidenemethyl)-4-(4-fluorophenyl)-1-(3-phenylpropyl)-1*H*-imidazol-5-yl]pyridineC₃₀ H₃₁ F N₄; Mol wt: 466.6009

ACTION – An inhibitor of the production of proinflammatory cytokines, particularly TNF-α and IL-1β, expected to be useful for the treatment of arthritis and other inflammatory conditions. It inhibited the production of TNF-α in peripheral blood mononuclear cells with an IC₅₀ of 17 nM. Following administration to mice, it was shown to prevent the lipopolysaccharide-stimulated production of TNF-α by 89 and 98%, respectively, at oral doses of 10 and 25 mg/kg. Another exemplified substituted imidazole derivative is:

**320789:** C₂₉ H₂₉ F N₄**SOURCE** – Ortho-McNeil.**REFERENCES**

1. Beers, S. and Wachter, M.P. (Ortho-McNeil Pharmaceutical, Inc.) *Substd. imidazoles useful in the treatment of inflammatory diseases*. WO 0232894.

3207982(*S*)-(4-Phenoxybenzamido)-3-(2-phenoxypropionamido)-propionohydroxamic acidC₂₅ H₂₅ N₃ O₆; Mol wt: 463.4875

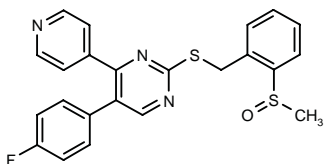
ACTION – Matrix metalloproteinase (MMP) inhibitor that displayed an IC₅₀ of 15.6 nM against MMP-13 (collagenase 3) and is also reported to inhibit the production of TNF-α. Potentially useful for the treatment of arthritis, cancer, tissue ulceration, restenosis, periodontal disease, epidermolysis bullosa, scleritis, psoriasis, AIDS and septic shock, among other disorders mediated by MMPs and TNF-α.

SOURCE – Fujisawa.**REFERENCES**

1. Sawada, A. and Neya, M. (Fujisawa Pharmaceutical Co., Ltd.) *MMP inhibitor*. WO 0230873.

320816

5-(4-Fluorophenyl)-2-[2-(methylsulfinyl)benzylsulfanyl]-4-(4-pyridyl)pyrimidine



C23 H18 F N3 O S2; Mol wt: 435.5452

ACTION – Cytokine release inhibitor able to inhibit TNF- α and IL-1 β production in peripheral blood mononuclear cells (IC_{50} = 3.2 and 2.3 μ M, respectively) and p38 MAP (mitogen-activated protein) kinase activity (IC_{50} = 5.1 μ M). Potentially useful for the treatment of chronic inflammatory diseases such as rheumatoid arthritis and inflammatory bowel disease.

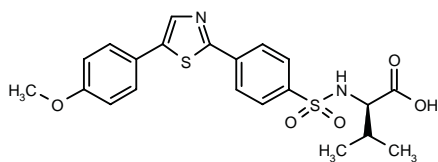
SOURCE – Universität Tübingen, Tübingen (DE).

REFERENCES

1. Laufer, S.A. and Wagner, G.K. *From imidazoles to pyrimidines: New inhibitors of cytokine release.* J Med Chem 2002, 45(13): 2733.

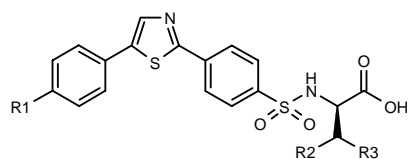
320822

N-[4-[5-(4-Methoxyphenyl)thiazol-2-yl]phenylsulfonyl]-D-valine



C21 H22 N2 O5 S2; Mol wt: 446.5458

ACTION – Matrix metalloproteinase (MMP) inhibitor that was shown to be active against MMP-2 (gelatinase A; IC_{50} = 0.347 nM), MMP-8 (neutrophil collagenase; IC_{50} = 6.47 nM), MMP-9 (gelatinase B; IC_{50} = 10.0 nM), MMP-12 (metalloelastase; IC_{50} = 0.370 nM) and MMP-13 (collagenase 3; IC_{50} = 1.16 nM). Potentially useful for the treatment of rheumatoid arthritis, chronic obstructive pulmonary disease, corneal ulcer, periodontitis, viral infection, obstructive arteriosclerosis, aortic aneurysm, atherosclerosis, restenosis, sepsis, coronary thrombosis, scleritis, multiple sclerosis, hepatic cirrhosis, open-angle glaucoma, retinopathy, psoriasis, diabetes, osteoporosis, cancer, Crohn's disease, malaria, etc. Other exemplified compounds are:



Compound	R1	R2	R3	Formula
320823	Br	Me	Me	C ₂₀ H ₁₉ BrN ₂ O ₄ S ₂
320824	Cl	3-indolyl	H	C ₂₆ H ₂₀ ClN ₃ O ₄ S ₂

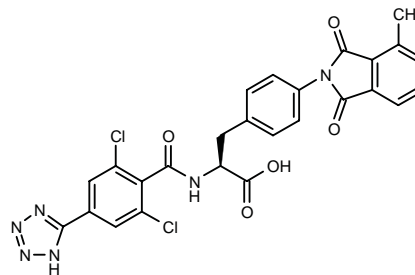
SOURCE – Shionogi.

REFERENCES

1. Watanabe, F. and Tamura, Y. (Shionogi & Co. Ltd.) *Thiazole or oxazole derivs.* WO 0228844.

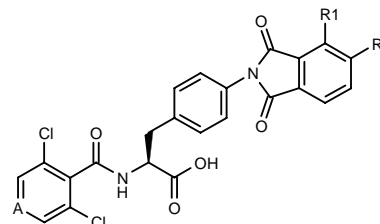
320831

N-[2,6-Dichloro-4-(1H-tetrazol-5-yl)benzoyl]-4-(4-methyl-1,3-dioxo-2,3-dihydro-1H-isoindol-2-yl)-L-phenylalanine



C26 H18 Cl2 N6 O5; Mol wt: 565.3712

ACTION – An antagonist of α_4 integrin found to inhibit the adhesion of VCAM-1 to $\alpha_4\beta_1$ -transfected Jurkat cells and $\alpha_4\beta_7$ -transfected RPMI-8866 cells with IC_{50} values of 0.0059 and 0.00055 μ M, respectively. Potentially useful for the treatment of rheumatoid arthritis, inflammatory bowel disease, systemic lupus erythematosus, multiple sclerosis, Sjögren's disease, asthma, psoriasis, allergy, diabetes, cardiovascular diseases, arteriosclerosis, restenosis, cancer and transplant rejection. Other exemplified phenylalanine derivatives are:



Compound	R1	R2	A	Formula
320832	H	NH2	CH	C ₂₄ H ₁₇ Cl ₂ N ₃ O ₅
320833	Me	H	N	C ₂₄ H ₁₇ Cl ₂ N ₃ O ₅
320834	H	H	-C(NHSO2Me)-	C ₂₆ H ₂₁ Cl ₂ N ₃ O ₇ S

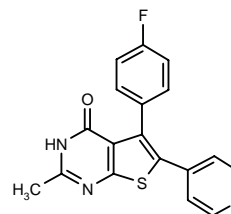
SOURCE – Ajinomoto.

REFERENCES

1. Suzuki, N. et al. (Ajinomoto Co., Inc.) *Novel phenylalanine derivs.* WO 0228830.

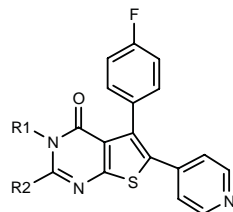
320837

5-(4-Fluorophenyl)-2-methyl-6-(4-pyridyl)thieno[2,3-d]pyrimidin-4(3H)-one

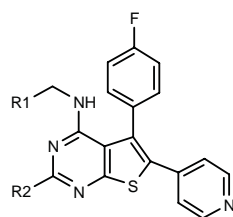


C18 H12 F N3 O S; Mol wt: 337.3768

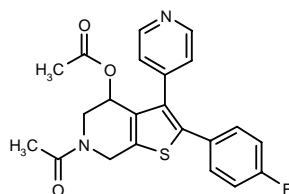
ACTION – Agent with the ability to inhibit the production of TNF- α , as demonstrated in rats by 94% inhibition of lipopolysaccharide-stimulated TNF- α production at a dose of 50 mg/kg p.o. In addition, it demonstrated no toxicity in mice at 10 mg/kg/day p.o. for 14 days. Potentially useful for the treatment of allergy, bronchial asthma, septic shock, inflammatory bowel disease, inflammation of organs, bone resorption, arthritis, diabetes, psoriasis, Crohn's disease, ulcerative colitis, malaria, inflammatory pulmonary diseases, thrombosis, AIDS, etc. Other exemplified thiophene-containing bicyclic compounds are:



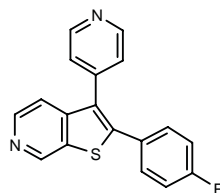
Compound	R1	R2	Formula
320838	H	H	C ₁₇ H ₁₀ FN ₃ OS
320840	Me	Me	C ₁₉ H ₁₄ FN ₃ OS



Compound	R1	R2	Formula
320839	CH ₂ OH	Me	C ₂₀ H ₁₇ FN ₄ OS
320843	CH ₂ OH	H	C ₁₉ H ₁₅ FN ₄ OS
320844	Ph	H	C ₂₄ H ₁₇ FN ₄ S



320841: C₂₂ H₁₉ F N₂ O₃ S



320842: C₁₈ H₁₁ F N₂ S

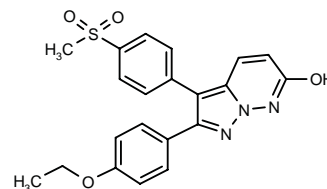
SOURCE – Nikken Chemicals.

REFERENCES

1. Fujita, S. et al. (Nikken Chemicals Co., Ltd.) *Novel bicyclic thiophene cpds.* JP 2002105081.

320917

2-(4-Ethoxyphenyl)-3-[4-(methylsulfonyl)phenyl]pyrazolo-[1,5-*b*]pyridazin-6-ol



C₂₁ H₁₉ N₃ O₄ S; Mol wt: 409.4641

ACTION – A representative compound from a series of cyclooxygenase type 2 (COX-2) inhibitors, considered to have potential in the treatment of pain, fever and inflammation.

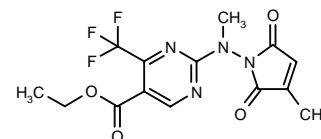
SOURCE – GlaxoSmithKline.

REFERENCES

1. Dear, G.J. and Gohil, K. (GlaxoSmithKline plc) *Chemical cpds.* WO 0232895.

320988

2-[*N*-Methyl-*N*-(3-methyl-2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)amino]-4-(trifluoromethyl)pyrimidine-5-carboxylic acid ethyl ester



C₁₄ H₁₃ F₃ N₄ O₄; Mol wt: 358.2747

ACTION – Potent inhibitor of AP-1- and NF- κ B-mediated gene expression in Jurkat T-cells. Potentially useful for the treatment of inflammatory diseases including asthma, psoriasis, rheumatoid arthritis and transplant rejection.

SOURCE – Signal (Celgene).

REFERENCES

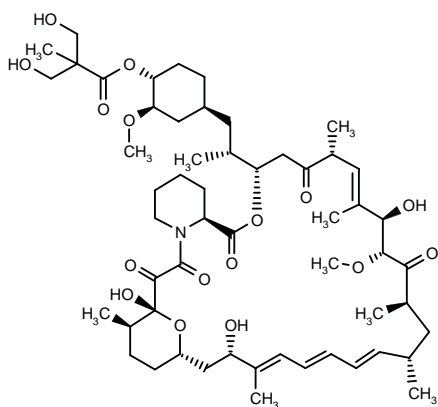
1. Suto, M.J. et al. (Signal Pharmaceuticals, Inc.) *Pyrimidine carboxylates and related cpds. and methods for treating inflammatory conditions.* JP 1999512390, US 5852028, WO 9709325.
2. Suto, M.J. et al. (Signal Pharmaceuticals, Inc.) *Pyrimidine carboxylates and related cpds. and methods for treating inflammatory conditions.* WO 9838171.
3. Shevlin, G.I. et al. *Structure-activity relationship studies of ethyl-2-[(3-methyl-2,5-dioxo(3-pyrrolinyl)amino]-4-(trifluoromethyl)pyrimides-5-carboxylate, an inhibitor of AP-1 and NF- κ B mediated gene expression.* 28th Natl Med Chem Symp (June 8-12, San Diego) 2002, Abst 27.

IMMUNOMODULATING AGENTS

320203

3-Hydroxy-2-(hydroxymethyl)-2-methylpropionic acid (1*R*,2*R*,4*S*)-4-[2(*R*)-[(3*S*,6*R*,9*R*,10*R*,12*R*,14*S*,21*S*,23*S*,26*R*,27*R*,34*aS*)-9,21,27-trihydroxy-10-methoxy-6,8,12,14,20,26-hexamethyl-1,5,11,28,29-pentaoso-3,4,5,6,9,10,11,12,13,14,21,22,23,24,25,26,27,28,29,31,32,33,34,34a-tetracosahydro-1*H*-23,27-epoxypyrido[2,1-*c*][1,4]oxazacyclohentricon-3-yl]propyl]-2-methoxycyclohexyl ester

3-Hydroxy-2-(hydroxymethyl)-2-methylpropionic acid 7-*O*-demethylrapamycin-42-yl ester



C55 H85 N O16; Mol wt: 1016.2680

ACTION – A representative compound from a series of 7-demethylrapamycin derivatives that acts as an immunosuppressant. It demonstrated *in vitro* activity against a panel of *Candida* and *Aspergillus* fungi, giving MIC values < 2 µg/ml against all the *Candida* spp. tested. When evaluated for antineoplastic activity against human glioblastoma U-87 MG cells, compound showed an IC₅₀ of 6.5 ng/ml. Potentially useful for the treatment of transplant rejection, solid tumors, fungal infections, rheumatoid arthritis, multiple sclerosis, restenosis and pulmonary inflammation.

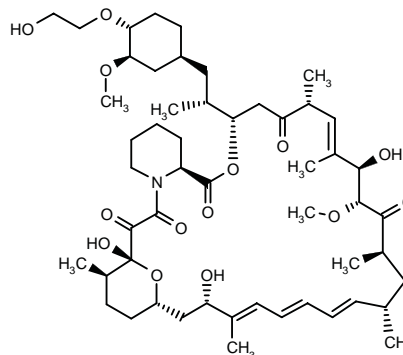
SOURCE – Wyeth.

REFERENCES

1. Zhu, T. and Enever, R. (American Home Products Corp.) *Hydroxyesters of 7-desmethylrapamycin*. US 6399626, WO 0228866.

320204

(3*S*,6*R*,9*R*,10*R*,12*R*,14*S*,21*S*,23*S*,26*R*,27*R*,34*aS*)-9,21,27-Trihydroxy-3-[2-[(1*S*,3*R*,4*R*)-4-(2-hydroxyethoxy)-3-methoxycyclohexyl]-1(*R*)-methylethyl]-10-methoxy-6,8,12,14,20,26-hexamethyl-3,4,5,6,9,10,11,12,13,14,21,22,23,24,25,26,27,28,29,31,32,33,34,34a-tetracosahydro-1*H*-23,27-epoxypyrido[2,1-*c*][1,4]oxazacyclohentricon-1,5,11,28,29-pentaone



C52 H81 N O14; Mol wt: 944.2049

ACTION – A representative compound from a series of 7-demethylrapamycin derivatives that acts as an immunosuppressant. It demonstrated *in vitro* activity against a panel of *Candida* and *Aspergillus* fungi, giving MIC values < 2 µg/ml against all the *Candida* spp. tested. When evaluated for antineoplastic activity against human glioblastoma U-87 MG cells, compound showed an IC₅₀ of 3.5 ng/ml. Potentially useful for the treatment of transplant rejection, solid tumors, fungal infections, rheumatoid arthritis, multiple sclerosis, restenosis and pulmonary inflammation.

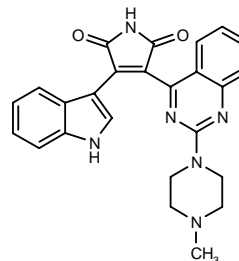
SOURCE – Wyeth.

REFERENCES

1. Zhu, T. and Enever, R. (American Home Products Corp.) *Ethers of 7-desmethylrapamycin*. US 2002061905, WO 0228867.

321045

3-(1*H*-Indol-3-yl)-4-[2-(4-methylpiperazin-1-yl)quinazolin-4-yl]-2,5-dihydro-1*H*-pyrrole-2,5-dione



C25 H22 N6 O2; Mol wt: 438.4888

ACTION – A preferred compound from a series of indolymaleimide derivatives that act as protein kinase C (PKC) inhibitors. Compound inhibited different PKC isoforms with IC₅₀ values between 8 and 50 nM. It also inhibited T-cell activation and proliferation with an IC₅₀ value of 168 nM in an allogeneic mixed lymphocyte reaction. Potentially useful for the treatment of graft rejection, cancer and autoimmune disorders.

SOURCE – Novartis.

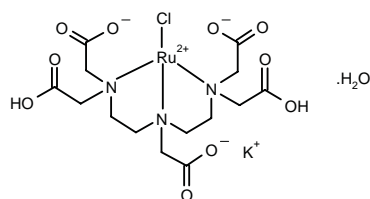
REFERENCES

1. Albert, R. et al. (Novartis AG; Novartis-Erfindungen VmbH) *Indolymaleimide derivs. as protein kinase C inhibitors*. WO 0238561.

AMD-6221

303353

Potassium dihydrogen (OC-6-45)-[N-[2-[bis[(carboxy-κO)methyl]amino-κN]ethyl]-N-[2-[bis(carboxymethyl)amino]ethyl]glycinato(5-)-κN,κO]chlororuthenate(3-) monohydrate



C14 H20 Cl K N3 O10 Ru . H2O; Mol wt: 583.9588

ACTION – Ruthenium-based nitric oxide scavenger able to inhibit nitrosylation of myocardial protein and to prolong cardiac allograft survival in a model of acute cardiac transplant rejection. In rats with cardiac allograft, compound administered alone (75 mg/kg i.p. b.i.d.) or in combination with low-dose ciclosporin was able to significantly prolong allograft survival compared to untreated or ciclosporin-treated animals. Potentially useful for the prevention of cardiac allograft rejection alone or in combination with ciclosporin in order to reduce the potential toxic side effects associated with immunosuppressant therapy. It has also been found to inhibit tumor growth via inhibition of angiogenesis in tumor-bearing rats.

SOURCE – AnorMED.

REFERENCES

1. Fricker, S. et al. (AnorMED Inc.) *Pharmaceutical compsns. comprising metal complexes*. EP 1163247, WO 0056743.
2. Mosi, R. et al. *Mechanistic studies on AMD6221: A ruthenium-based nitric oxide scavenger*. Biochem Biophys Res Commun 2002, 292(2): 519.
3. Pieper, G.M. et al. *A novel scavenger of nitric oxide decreases heme protein nitrosylation and prolongs graft survival during cardiac transplant rejection*. J Heart Lung Transplant 2001, 20(2): 157.
4. Pieper, G.M. et al. *A ruthenium (III) polyaminocarboxylate complex, a novel nitric oxide scavenger, enhances graft survival and decreases nitrosylated heme protein in models of acute and delayed cardiac transplant rejection*. J Cardiovasc Pharmacol 2002, 39(3): 441.
5. Pritchard, R. et al. *Ruthenium-based nitric oxide scavengers inhibit tumour growth by reducing tumor vasculature*. Clin Exp Metastasis 1999, 17(9): 776.

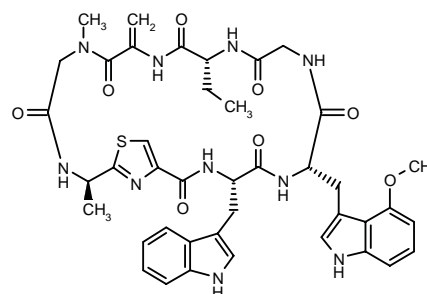
6. Roza, A.M. et al. *AMD6221, a novel nitric oxide scavenger, decreases heme protein nitrosylation and prolongs cardiac allograft survival*. Am J Transplant 2001, 1(Suppl. 1): Abst 365.

7. Yasuda, N. et al. *Pharmacokinetics and tissue distribution of a ruthenium-based nitric oxide scavenger in the rat*. Int J Toxicol 2000, 19(6): 22.

ARGYRIN B

320769

(4S,7S,13R,22R)-13-Ethyl-4-(1H-indol-3-ylmethyl)-7-(4-methoxy-1H-indol-3-ylmethyl)-18,22-dimethyl-16-methylene-24-thia-3,6,9,12,15,18,21,26-octazabicyclo[21.2.1]-hexacosa-1(25),23(26)-diene-2,5,8,11,14,17,20-heptaone



C41 H46 N10 O8 S; Mol wt: 838.9424

ACTION – Immunosuppressant cyclic heptapeptide isolated from the myxobacterium *Archangium gephyra* strain Ar 8082 and subsequently synthesized. Compound strongly inhibited T-cell-independent antibody formation and CD40L-induced IgG production in murine and human B-cells. It also inhibited the murine mixed lymphocyte reaction (MLR), a cellular-based model for alloantigenic-mediated T-cell activation and proliferation. No cytotoxicity against human Jurkat T-cells was seen. Potentially useful for the treatment of transplant rejection.

SOURCES – GNF; Novartis.

REFERENCES

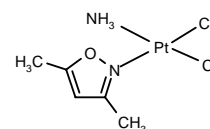
1. Ley, S.V. et al. *Total synthesis of the cyclic heptapeptide argirin B: A new potent inhibitor of T-cell independent antibody formation*. Org Lett 2002, 4(5): 711.
2. Sasse, F. et al. *Argyrins, immunosuppressive cyclic peptides from myxobacteria. I. Production, isolation, physico-chemical and biological properties*. J Antibiot 2002, 55(6): 543.

ONCOLYTIC DRUGS

DNA-DAMAGING DRUGS

320133

Amminedichloro(3,5-dimethylisoxazole)platinum(II)



C5 H10 Cl2 N2 Pt; Mol wt: 380.1330

ACTION – A preferred compound from a series of indolylmaleimide derivatives that act as protein kinase C (PKC) inhibitors. Compound inhibited different PKC isoforms with IC_{50} values between 8 and 50 nM. It also inhibited T-cell activation and proliferation with an IC_{50} value of 168 nM in an allogeneic mixed lymphocyte reaction. Potentially useful for the treatment of graft rejection, cancer and autoimmune disorders.

SOURCE – Novartis.

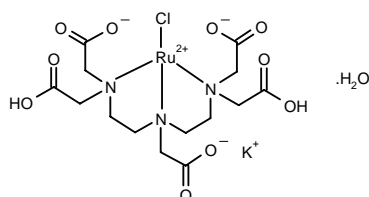
REFERENCES

1. Albert, R. et al. (Novartis AG; Novartis-Erfindungen VmbH) *Indolylmaleimide derivs. as protein kinase C inhibitors*. WO 0238561.

AMD-6221

303353

Potassium dihydrogen (*OC-6-45*)-[*N*-[2-[bis[(carboxy- κ O)methyl]amino- κ N]ethyl]-*N*-[2-[bis(carboxymethyl)amino]ethyl]glycinato(5-)- κ N, κ O]chlororuthenate(3-) monohydrate



C14 H20 Cl K N3 O10 Ru . H2O; Mol wt: 583.9588

ACTION – Ruthenium-based nitric oxide scavenger able to inhibit nitrosylation of myocardial protein and to prolong cardiac allograft survival in a model of acute cardiac transplant rejection. In rats with cardiac allograft, compound administered alone (75 mg/kg i.p. b.i.d.) or in combination with low-dose ciclosporin was able to significantly prolong allograft survival compared to untreated or ciclosporin-treated animals. Potentially useful for the prevention of cardiac allograft rejection alone or in combination with ciclosporin in order to reduce the potential toxic side effects associated with immunosuppressant therapy. It has also been found to inhibit tumor growth via inhibition of angiogenesis in tumor-bearing rats.

SOURCE – AnorMED.

REFERENCES

1. Fricker, S. et al. (AnorMED Inc.) *Pharmaceutical compsns. comprising metal complexes*. EP 1163247, WO 0056743.
2. Mosi, R. et al. *Mechanistic studies on AMD6221: A ruthenium-based nitric oxide scavenger*. Biochem Biophys Res Commun 2002, 292(2): 519.
3. Pieper, G.M. et al. *A novel scavenger of nitric oxide decreases heme protein nitrosylation and prolongs graft survival during cardiac transplant rejection*. J Heart Lung Transplant 2001, 20(2): 157.
4. Pieper, G.M. et al. *A ruthenium (III) polyaminocarboxylate complex, a novel nitric oxide scavenger, enhances graft survival and decreases nitrosylated heme protein in models of acute and delayed cardiac transplant rejection*. J Cardiovasc Pharmacol 2002, 39(3): 441.
5. Pritchard, R. et al. *Ruthenium-based nitric oxide scavengers inhibit tumour growth by reducing tumor vasculature*. Clin Exp Metastasis 1999, 17(9): 776.

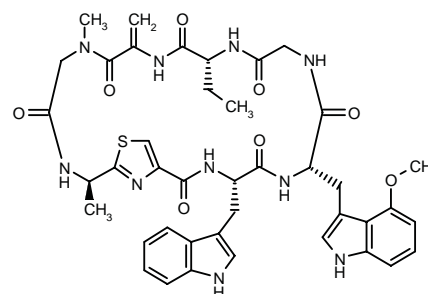
6. Roza, A.M. et al. *AMD6221, a novel nitric oxide scavenger, decreases heme protein nitrosylation and prolongs cardiac allograft survival*. Am J Transplant 2001, 1(Suppl. 1): Abst 365.

7. Yasuda, N. et al. *Pharmacokinetics and tissue distribution of a ruthenium-based nitric oxide scavenger in the rat*. Int J Toxicol 2000, 19(6): 22.

ARGYRIN B

320769

(4*S*,7*S*,13*R*,22*R*)-13-Ethyl-4-(1*H*-indol-3-ylmethyl)-7-(4-methoxy-1*H*-indol-3-ylmethyl)-18,22-dimethyl-16-methylene-24-thia-3,6,9,12,15,18,21,26-octazabicyclo[21.2.1]-hexacos-1(25),23(26)-diene-2,5,8,11,14,17,20-heptaone



C41 H46 N10 O8 S; Mol wt: 838.9424

ACTION – Immunosuppressant cyclic heptapeptide isolated from the myxobacterium *Archangium gephyra* strain Ar 8082 and subsequently synthesized. Compound strongly inhibited T-cell-independent antibody formation and CD40L-induced IgG production in murine and human B-cells. It also inhibited the murine mixed lymphocyte reaction (MLR), a cellular-based model for alloantigenic-mediated T-cell activation and proliferation. No cytotoxicity against human Jurkat T-cells was seen. Potentially useful for the treatment of transplant rejection.

SOURCES – GNF; Novartis.

REFERENCES

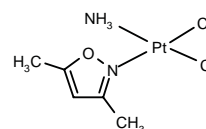
1. Ley, S.V. et al. *Total synthesis of the cyclic heptapeptide argyirin B: A new potent inhibitor of T-cell independent antibody formation*. Org Lett 2002, 4(5): 711.
2. Sasse, F. et al. *Argyirins, immunosuppressive cyclic peptides from myxobacteria. I. Production, isolation, physico-chemical and biological properties*. J Antibiot 2002, 55(06): 543.

ONCOLYTIC DRUGS

DNA-DAMAGING DRUGS

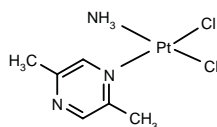
320133

Amminedichloro(3,5-dimethylisoxazole)platinum(II)

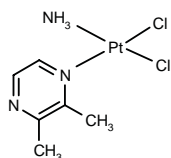


C5 H10 Cl2 N2 Pt; Mol wt: 380.1330

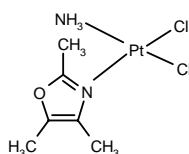
ACTION – Antineoplastic platinum complex with *in vitro* activity against a panel of cancer cell lines including cisplatin-resistant strains. The solubility in water of this compound was determined to be 1.27 mg/ml. Other exemplified complexes are:



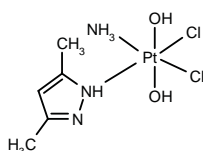
320134: C6 H11 Cl2 N3 Pt



320135: C6 H11 Cl2 N3 Pt



320136: C6 H12 Cl2 N2 O Pt



320137: C5 H13 Cl2 N3 O2 Pt

SOURCE – AnorMED.

REFERENCES

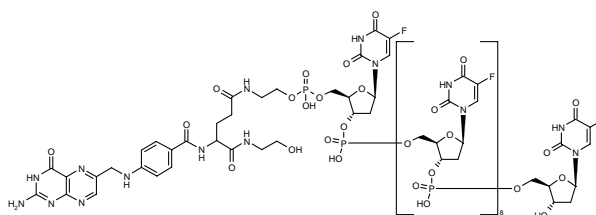
1. Wong, E.S.Y. and Giandomenico, C.M. (AnorMED Inc.) *Platinum complexes as antitumor agents*. WO 0228871.

ANTIMETABOLITES

FA-FdUMP[10]

320321

2'-Deoxy-5-fluorocytidylyl-(3'→5')-2'-deoxy-5-fluorocytidylyl-(3'→5')-2'-deoxy-5-fluorocytidylyl-(3'→5')-2'-deoxy-5-fluorocytidylyl-(3'→5')-2'-deoxy-5-fluorocytidylyl-(3'→5')-2'-deoxy-5-fluorocytidylyl-(3'→5')-2'-deoxy-5-fluorocytidylyl-(3'→5')-2'-deoxy-5-fluorocytidylic acid 2-[4-[4-(2-amino-4-oxo-3,4-dihydropteridin-6-yl-methylamino)benzamido]-5-(2-hydroxyethylamino)-5-oxopentanamido]ethyl ester



C113 H129 F10 N29 O76 P10; Mol wt: 3609.1090

ACTION – Targeted cytotoxic agent, a folic acid conjugated to a 10-mer oligodeoxyribonucleotide with improved cytotoxicity against 5-fluorouracil (5-FU)-sensitive and -resistant human colorectal cancer H630 cells (IC₅₀ = 0.054-0.089 and 0.18-0.58 nM, respectively).

SOURCE – University of Nebraska Medical Center, Omaha, NE (US).

REFERENCES

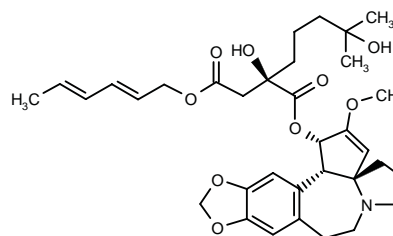
1. Liu, J. et al. *Targeted drug delivery to chemoresistant cells: Folic acid derivatization of FdUMP[10] enhances cytotoxicity toward 5-FU-resistant human colorectal tumor cells*. J Org Chem 2001, 66(17): 5655.

ANTIBIOTICS AND ALKALOIDS

320603

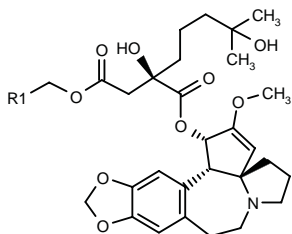
2(*R*)-Hydroxy-2-(4-hydroxy-4-methylpentyl)succinic acid 1-(cephalotaxin-3-yl) 4-(2,4-hexadienyl) diester

3-[2(*R*)-[2-(2,4-Hexadienyloxy)-2-oxoethyl]-2,6-dihydroxy-6-methylheptanoyloxy]cephalotaxine

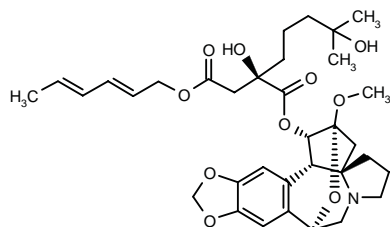


C34 H45 N O9; Mol wt: 611.7275

ACTION – A cephalotaxane derivative expected to be useful for the treatment of cancer, harringtonine-resistant leukemia and parasitic infections. It was shown to be 4-, 8.5- and 570-fold more active than homoharringtonine, harringtonine and cephalotaxine, respectively, against the myeloid leukemia K-562 cell line, and it displayed an IC_{50} of 16 ng/ml against homoharringtonine-resistant K-562/MRP cells. Other exemplified compounds are:



Compound	R1	Formula
320605	C5H11	C ₃₄ H ₄₉ NO ₉
320606	C(Me)=CH ₂	C ₃₂ H ₄₃ NO ₉
320607	CH ₂ CH ₂ CH=CHMe	C ₃₄ H ₄₇ NO ₉



320608: C₃₄ H₄₅ N O₁₀

SOURCE – OncoPharm.

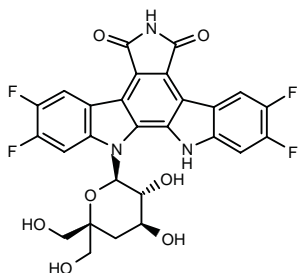
REFERENCES

1. Robin, J.-P. et al. (OncoPharm Corp.) *New cephalotaxanes, their method of preparation and their use in treatment of cancers, leukemias, parasites including those resistant to usual chemotherapeutic agents and as reversal agents.* WO 0232904.

DNA-INTERCALATING DRUGS

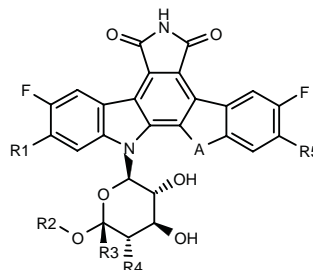
320114

12-[4-Deoxy-5-(hydroxymethyl)- β -D-glucopyranosyl]-2,3,9,10-tetrafluoro-6,7,12,13-tetrahydro-5H-indolo[2,3-a]pyrrolo[3,4-c]carbazole-5,7-dione



C₂₇ H₁₉ F₄ N₃ O₇; Mol wt: 573.4531

ACTION – Antitumor agent, a DNA topoisomerase I inhibitor (IC_{50} = 0.04 μ M) that prevented the proliferation of murine P388 cells with an IC_{50} of 0.035 μ M. Other exemplified compounds are:



Compound	R1	R2	R3	R4	R5	A	Formula
320115	F	Me	Me	H	F	NH	C ₂₇ H ₁₉ F ₄ N ₃ O ₆
320116	F	Me	CH ₂ OH	OH	F	NH	C ₂₇ H ₁₉ F ₄ N ₃ O ₈
320118	F	Me	CH ₂ OH	H	F	NH	C ₂₇ H ₁₉ F ₄ N ₃ O ₇
320119	H	Me	Me	H	H	NH	C ₂₇ H ₂₁ F ₂ N ₃ O ₆
320120	H	Et	Me	H	H	NH	C ₂₈ H ₂₃ F ₂ N ₃ O ₆
320121	H	i-Pr	Me	H	H	NH	C ₂₉ H ₂₅ F ₂ N ₃ O ₆
320122	F	Me	Me	H	F	S	C ₂₇ H ₁₈ F ₄ N ₂ O ₆ S

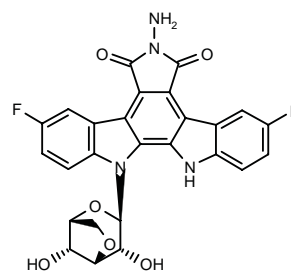
SOURCE – Bristol-Myers Squibb.

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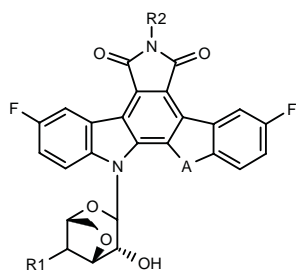
320546

6-Amino-12-(3,6-anhydro- β -D-glucopyranosyl)-3,9-difluoro-6,7,12,13-tetrahydro-5H-indolo[2,3-a]pyrrolo[3,4-c]carbazole-5,7-dione

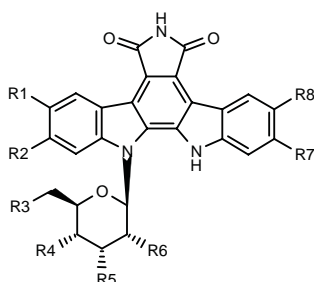


C₂₆ H₁₈ F₂ N₄ O₆; Mol wt: 520.4462

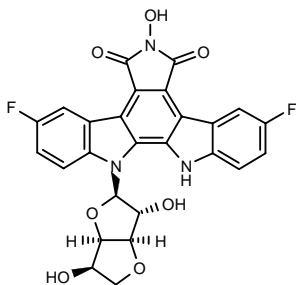
ACTION – DNA topoisomerase I inhibitor (IC_{50} = 0.01 μ M) shown to inhibit the proliferation of murine leukemia P388 cells with an IC_{50} < 0.003 μ M. Other exemplified indolo-carbazoles are:



Compound	R1	R2	A	Isomer	Formula
320547	OH	H	NH	1R,4R	C ₂₆ H ₁₇ F ₂ N ₃ O ₆
320548	OH	H	NH	1S,4R	C ₂₆ H ₁₇ F ₂ N ₃ O ₆
320549	OH	OH	NH	1R,4R	C ₂₆ H ₁₇ F ₂ N ₃ O ₇
320553	H	H	NH	1R	C ₂₆ H ₁₇ F ₂ N ₃ O ₅
320555	OH	H	S	1S,4R	C ₂₆ H ₁₆ F ₂ N ₂ O ₆ S
320556	OH	H	NH	1R,4S	C ₂₆ H ₁₇ F ₂ N ₃ O ₆



Compound	R1	R2	R3	R4	R5	R6	R7	R8	Formula
320551	F	H	F	F	-O-	H	F	F	C ₂₆ H ₁₅ F ₄ N ₃ O ₄
320552	F	H	OH	-O-	OH	H	F	F	C ₂₆ H ₁₇ F ₂ N ₃ O ₆
320554	H	F	OH	-O-	OH	F	H	H	C ₂₆ H ₁₇ F ₂ N ₃ O ₆



320550: C₂₆ H₁₇ F₂ N₃ O₇

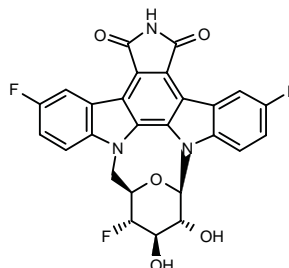
SOURCE – Bristol-Myers Squibb.

REFERENCES

1. Saulnier, M.G. et al. (Bristol-Myers Squibb Co.) *Anhydro sugar derivs. of indolocarbazoles*. WO 0230942.

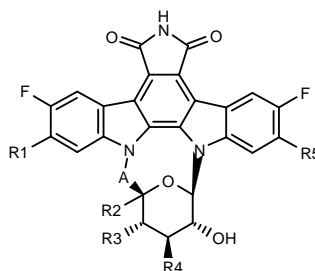
320557

(6*R*,7*R*,8*S*,9*S*,10*R*)-2,9,15-Trifluoro-7,8-dihydroxy-7,8,9,10,11,17,18,19-octahydro-6*H*-6,10-epoxydiindolo-[1,2,3-*hi*:3',2',1'-*mn*]pyrrolo[3,4-*k*][1,8]benzodiazecine-17,19-dione

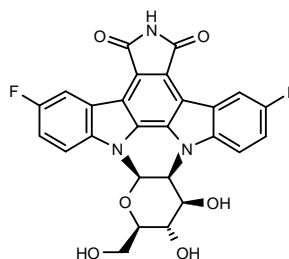


C₂₆ H₁₆ F₃ N₃ O₅; Mol wt: 507.4224

ACTION – DNA topoisomerase I inhibitor (IC₅₀ = 0.028 μM) shown to inhibit the proliferation of murine leukemia P388 cells with an IC₅₀ of 0.003 μM. Other exemplified indolylpyrrolocarbazoles are:



Compound	R1	R2	R3	R4	R5	A	Formula
320558	F	Me	OH	OH	F	bond	C ₂₆ H ₁₅ F ₄ N ₃ O ₆
320559	F	CH ₂ OH	OH	OH	F	bond	C ₂₆ H ₁₅ F ₄ N ₃ O ₇
320561	F	H	OH	OH	F	-CH ₂ -	C ₂₆ H ₁₅ F ₄ N ₃ O ₆
320562	F	H	F	OH	F	-CH ₂ -	C ₂₆ H ₁₄ F ₅ N ₃ O ₆
320563	F	H	OH	H	F	-CH ₂ -	C ₂₆ H ₁₅ F ₄ N ₃ O ₅
320564	H	H	OH	OH	H	-CH ₂ -	C ₂₆ H ₁₇ F ₂ N ₃ O ₆



320565: C₂₆ H₁₇ F₂ N₃ O₆

SOURCE – Bristol-Myers Squibb.

REFERENCES

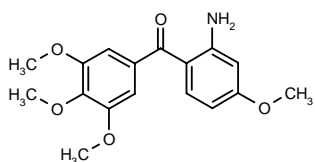
1. Saulnier, M.G. et al. (Bristol-Myers Squibb Co.) *Topoisomerase inhibitors*. WO 0230941.

ANTIMITOTIC DRUGS

319380

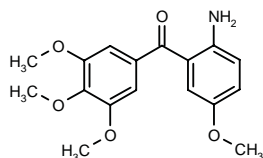
1-(2-Amino-4-methoxyphenyl)-1-(3,4,5-trimethoxyphenyl)methanone

2-Amino-3',4,4',5'-tetramethoxybenzophenone



C17 H19 N O5; Mol wt: 317.3391

ACTION – Antimitotic agent, an analogue of combretastatin A4 with improved growth-inhibitory activity against a panel of human cancer cells including colon adenocarcinoma COLO 205, stomach cancer NUGC3 and liver cancer HA22T cells (IC_{50} = 17, 80 and 48 nM, respectively, vs. 2756, 8520 and 2708 nM, respectively, for combretastatin A4). It was shown to compete with colchicine for binding to tubulin and to cause significant arrest of cells at the G_2/M phase of the cell cycle. Another related compound is:



319381: C17 H19 N O5

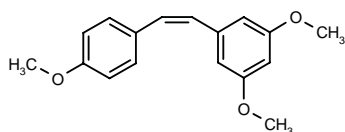
SOURCE – National Health Research Institutes, Taipei (TW).

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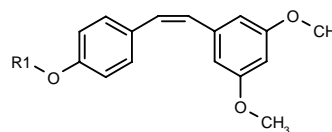
319386

cis-3,4',5'-Trimethoxystilbene



C17 H18 O3; Mol wt: 270.3262

ACTION – Antineoplastic agent, a resveratrol derivative with improved cytotoxicity against human cancer cell lines including pancreatic cancer BxPC-3, breast adenocarcinoma MCF7, non-small cell lung cancer NCI-H460 and prostate cancer DU 145 cells (IC_{50} = 2.8-5.4 ng/ml). Compound showed antimitotic activity (IC_{50} = 1.8 μ M for inhibition of tubulin polymerization) and inhibited colchicine binding by 95% at 5 μ M. Other related compounds are:



Compound	R1	Formula
319387	H	$C_{16}H_{16}O_3$
Resverastatin phosphate sodium [319388]	PO(ONa)2	$C_{16}H_{15}Na_2O_6P$

SOURCES – Arizona State University, Tempe, AZ (US); National Institutes of Health, Bethesda, MD (US).

REFERENCES

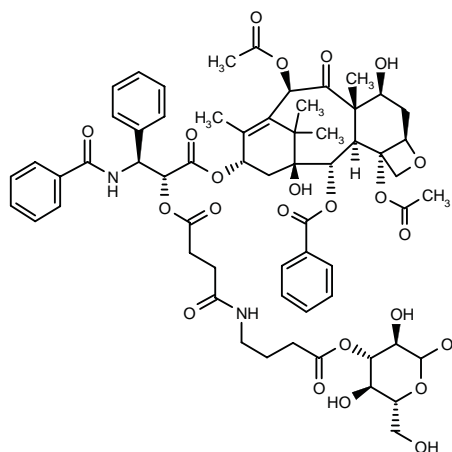
1. Pettit, G.R. et al. *Antineoplastic agents*. 465. *Structural modification of resveratrol: Sodium resverastatin phosphate*. J Med Chem 2002, 45(12): 2534.

CHACKOL

320996

Benzoic acid (2a*R*,4*S*,4a*S*,6*R*,9*S*,11*S*,12*S*,12a*R*,12b*S*)-6,12b-diacetoxy-9-[3(*S*)-benzamido-2(*R*)-[3-[*N*-[4-oxo-4-(β -glucopyranosyloxy)butyl]carbamoyl]propionyloxy]-3-phenylpropionyloxy]-4,11-dihydroxy-4a,8,13,13-tetramethyl-5-oxo-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-1*H*-7,11-methanocyclodeca[3,4]benzo-[1,2-*b*]oxet-12-yl ester

2'-*O*-[3-[*N*-[4-(β -Glucopyranos-3-yloxy)-4-oxobutyl]-carbamoyl]propionyl]paclitaxel



C61 H72 N2 O23; Mol wt: 1201.2310

ACTION – Antineoplastic agent, a paclitaxel-glucose conjugate with improved cytotoxicity and solubility compared with the parent drug. In the ovarian cancer cell lines OVCAR-3, OVCAR-5 and IGROV-1 it was 18-, 32-, and 45-fold more active than paclitaxel and exhibited a GI_{50} value in the subnanomolar range; against the breast cancer lines MCF7, BT-549 and T-47D, it was 5-23 times more active than paclitaxel.

SOURCE – Organomed.

REFERENCES

1. Jacob, J.N. (Organomed Corporation) *Paclitaxel-carbohydrate conjugates: Design, synthesis and biological evaluations*. US 6218367.

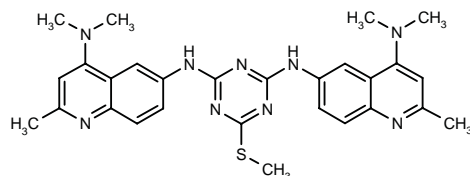
2. Jacob, J.N. *Synthesis and biological studies of a paclitaxel-glucose conjugate as potent anticancer agent*. 28th Natl Med Chem Symp (June 8-12, San Diego) 2002, Abst 47.

COMPOUND 115405

306193

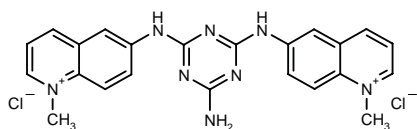
6,6'-[6-(Methylsulfanyl)-1,3,5-triazin-2,4-diyl]bis(imino)-bis(*N,N,N*,2-trimethylquinolin-4-amine)

2,4-Bis[4-(dimethylamino)-2-methylquinolin-6-ylamino]-6-(methylsulfanyl)-1,3,5-triazine



C₂₈ H₃₁ N₉ S; Mol wt: 525.6819

ACTION – Antineoplastic agent, a G-quadruplex DNA ligand with antitelomerase activity (IC₅₀ = 3 μM), able to stabilize the telomeric quadruplex. Long-term incubation of cancer cells induced growth arrest associated with telomere erosion and the appearance of the senescent cell phenotype. Compound inhibited the proliferation of a panel of human cancer cells with IC₅₀ values of 0.072-2.04 μM. Another related compound is:



Compound 12459 [306195]: C₂₃ H₂₂ Cl₂ N₈

SOURCE – Aventis Pharma.

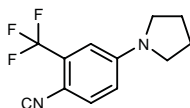
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- Riou, J.F. et al. *Cell senescence and telomere shortening induced by a new series of specific G-quadruplex DNA ligands*. Proc Natl Acad Sci USA 2002, 99(5): 2672.

HORMONAL AGENTS

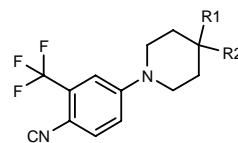
320062

4-(1-Pyrrolidinyl)-2-(trifluoromethyl)benzonitrile

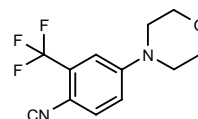


C₁₂ H₁₁ F₃ N₂; Mol wt: 240.2269

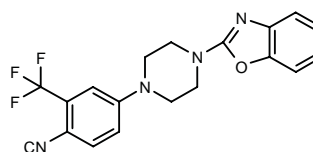
ACTION – Antiandrogen for use in the treatment of prostatic cancer, prostatic hypertrophy, virilism, hypertrichosis, baldness, acne and seborrhea. This compound prevented the DHT-induced transcriptional activation of human androgen receptors in CHO cells with an IC₅₀ of 0.14 μM. Other exemplified compounds are:



Compound	R1	R2	Formula
320065	H	OH	C ₁₃ H ₁₃ F ₃ N ₂ O
320066	H	OEt	C ₁₅ H ₁₇ F ₃ N ₂ O
320067	-O-		C ₁₃ H ₁₁ F ₃ N ₂ O
320068	H	4-F-Ph-NHCONHCH ₂	C ₂₁ H ₂₀ F ₄ N ₄ O
320069	H	4-F-Ph-NHCONH	C ₂₀ H ₁₈ F ₄ N ₄ O



320064: C₁₂ H₁₁ F₃ N₂ O



320070: C₁₉ H₁₅ F₃ N₄ O

SOURCE – Yamanouchi.

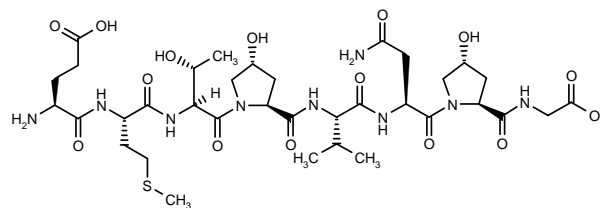
REFERENCES

- Taniguchi, N. et al. (Yamanouchi Pharmaceutical Co., Ltd.) *Anti-androgen agents*. JP 2002088073.

AFPep

302163

L-Glutamyl-L-methionyl-L-threonyl-4(*R*)-hydroxy-L-prolyl-L-valyl-L-asparaginyl-4(*R*)-hydroxy-L-prolyl-glycine



C₃₅ H₅₇ N₉ O₁₅ S; Mol wt: 875.9493

ACTION – α-Fetoprotein-derived peptide able to prevent the growth of estrogen receptor-positive MCF7 and T-47D human breast cancer xenografts in mice at 1 μg b.i.d. i.p., with an effect comparable to that of tamoxifen at 50 μg s.c. It was also active against tamoxifen-resistant MCF7 but not tamoxifen-resistant MDA-MB-231 xenografts. In mice, the peptide had no uterotrophic effects when given alone, but it inhibited the uterotrophic side effects of tamoxifen and estradiol. The peptide did not compete with estradiol receptors and did not reduce serum estradiol levels; preliminary studies showed that it reduced the levels of MAPK kinase, thereby preventing the phosphorylation of estrogen receptors. Potentially useful for the treatment of breast cancer.

SOURCE – Albany Medical College, Albany, NY (US).

REFERENCES

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FULVESTRANT

Prop INN, USAN

177872

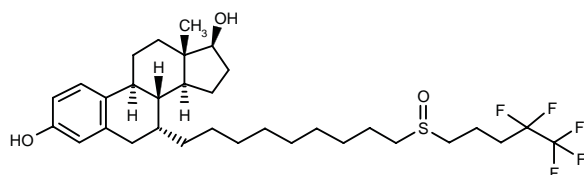
7 α -[9-(4,4,5,5,5-Pentafluoropentylsulfanyl)nonyl]estra-1,3,5(10)-triene-3,17 β -diol

ICI-182780⁺

ZD-182780

ZD-9238

ZM-182780



C32 H47 F5 O3 S; Mol wt: 606.7860

ACTION – Estrogen receptor antagonist.

INDICATION – Treatment of hormone receptor-positive, metastatic breast cancer in postmenopausal women with disease progression following antiestrogen therapy.

PRESENTATION – Solution for injection, 50 mg/ml.

PROPRIETARY NAME – *Faslodex* (US).

SOURCE – AstraZeneca.

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*Drug Data Rep 1992, 014(01): 0075.

CANCER IMMUNOTHERAPY

4B5 scFv

320739

Single-chain Fv form (ScFv) of the antiidiotypic human monoclonal antibody 4B5

ACTION – Cancer vaccine, a single-chain human antiidiotypic monoclonal antibody that mimics the GD2 antigen overexpressed on melanoma, neuroblastoma and small cell lung cancers. In mice, the vaccine induced both humoral and cell-mediated immune responses.

SOURCE – Viventia Biotech.

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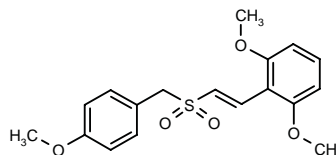
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INHIBITORS OF SIGNAL TRANSDUCTION PATHWAYS

319692

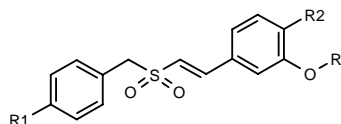
1,3-Dimethoxy-2-[(E)-2-(4-methoxybenzylsulfonyl)-vinyl]benzene

[(E)-2-(2,6-Dimethoxyphenyl)vinyl](4-methoxybenzyl)-sulfone



C18 H20 O5 S; Mol wt: 348.4170

ACTION – Antitumor agent displaying a GI_{50} of 200 nM against the pancreatic carcinoma MIA PaCa-2 cell line, while not inducing cell death in normal cells. Compound is reported to act through an interaction with the MAPK (mitogen-activated protein kinase) signal transduction pathway, and is also potentially useful for the treatment of other proliferative disorders such as hemangiomas in newborns, multiple sclerosis, chronic progressive myelodegenerative diseases, neurofibromatosis, ganglioneuromatosis, Paget's disease, fibrocystic diseases, sarcoidosis, cirrhosis, atherosclerosis and vascular restenosis. Other specifically claimed benzylsulfones are:



Compound	R1	R2	R3	Formula
319693	Cl	NO2	H	C ₁₅ H ₁₂ ClNO ₅ S
319695	OMe	OEt	Me	C ₁₉ H ₂₂ O ₅ S

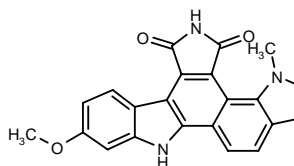
SOURCE – Temple University, Philadelphia, PA (US).

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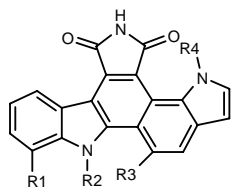
319841

9-Methoxy-3-methyl-4,5,6,11-tetrahydro-3H-indolo[6,7-a]-pyrrolo[3,4-c]carbazole-4,6-dione

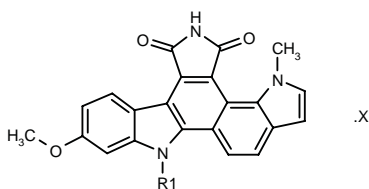


C22 H15 N3 O3; Mol wt: 369.3785

ACTION – Cyclin-dependent kinase CDK4 inhibitor with cytotoxic activity against human colon carcinoma HCT 116 ($IC_{50} = 1.80 \mu M$) and human non-small cell lung carcinoma NCI-H460 cells ($IC_{50} = 1.09 \mu M$). Potentially useful for the treatment of proliferative diseases including cancer. Other exemplified compounds include the following:



Compound	R1	R2	R3	R4	Formula
319842	H	H	H	Me	$C_{21}H_{13}N_3O_2$
319844	H	H	H	H	$C_{20}H_{11}N_3O_2$
319846	H	(CH ₂) ₃ OH	F	Me	$C_{24}H_{18}FN_3O_3$
319852	4-Me-1-Piz-CH ₂ CH ₂	H	H	Me	$C_{28}H_{27}N_5O_2$
319853	4-Me-1-Piz-(CH ₂) ₃	H	H	Me	$C_{29}H_{29}N_5O_2$
319854	1-Pip-CH ₂ CH ₂	H	H	Me	$C_{28}H_{26}N_4O_2$



Compound	R1	X	Formula
319845	(CH ₂) ₃ OH		$C_{25}H_{21}N_3O_4$
319848	4-(NH ₂ CO)-1-Pip-CH ₂ CH ₂		$C_{30}H_{29}N_5O_4$
319849	(CH ₂) ₃ NHCH ₂ CH ₂ N(Me) ₂		$C_{29}H_{31}N_5O_3$
319850	(CH ₂) ₃ NHCH ₂ CH ₂ N(Me) ₂	2HCl	$C_{29}H_{31}N_5O_3 \cdot 2HCl$
319851	(CH ₂) ₃ -L-Ala-OMe		$C_{29}H_{28}N_4O_5$

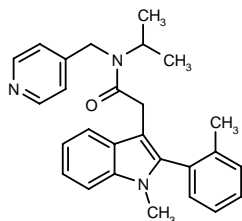
SOURCE – Lilly.

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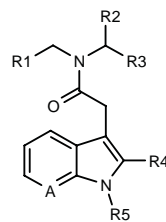
320098

N-Isopropyl-2-[1-methyl-2-(2-methylphenyl)-1*H*-indol-3-yl]-*N*-(pyridin-4-ylmethyl)acetamide

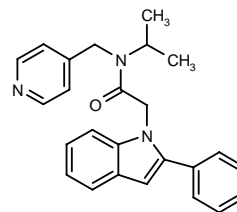


C₂₇ H₂₉ N₃ O; Mol wt: 411.5461

ACTION – Prenyltransferase, particularly protein farnesyltransferase and protein geranylgeranyltransferase type I, inhibitor. Potentially useful for the treatment of cancer, and also blindness related to retinal vascularization, hepatitis delta and related viral infections, restenosis and polycystic kidney disease. Other exemplified compounds are:



Compound	R1	R2	R3	R4	R5	A	Formula
320099	4-Pyr	Me	Me	H	2-Br-PhCH2	CH	C ₂₆ H ₂₆ BrN ₃
320101	4-Pyr	Me	Me	Ph	H	N	C ₂₄ H ₂₄ N ₄ O
320102	3-Pyr	-CH2CH2-		Ph	H	CH	C ₂₅ H ₂₃ N ₃ O
320103	vinyl	H	vinyl	Ph	H	CH	C ₂₂ H ₂₂ N ₂ O
320104	3-furyl	Me	Me	Ph	H	CH	C ₂₄ H ₂₄ N ₂ O ₂
320105	CH2CN	-CH2CH2-		Ph	H	CH	C ₂₂ H ₂₁ N ₃ O



320100: C₂₅ H₂₅ N₃ O

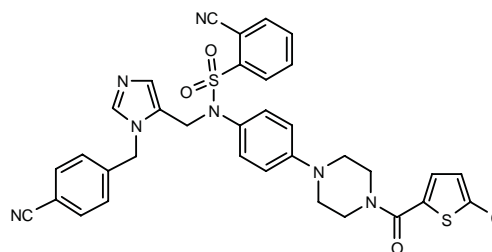
SOURCE – Merck & Co.

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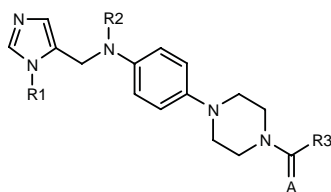
320278

N-[4-[4-(5-Chlorothien-2-ylcarbonyl)piperazin-1-yl]-phenyl]-2-cyano-*N*-[1-(4-cyanobenzyl)-1*H*-imidazol-5-ylmethyl]benzenesulfonamide



C₃₄ H₂₈ Cl N₇ O₃ S₂; Mol wt: 682.2262

ACTION – Protein farnesyltransferase inhibitor with an IC_{50} of 0.9 nM and > 10,000-fold selectivity over protein geranylgeranyltransferase. Potentially useful for the treatment of cancer, restenosis, atherosclerosis, hepatitis delta viral infections and benign proliferative disorders. Other exemplified compounds include the following:



Compound	R1	R2	R3	A	Formula
320279	H	SO ₂ Ph	i-BuNH	S	C ₂₅ H ₃₂ N ₆ O ₂ S ₂
320280	H	CONHPr	5-Cl-2-thienyl	O	C ₂₃ H ₂₇ ClN ₆ O ₂ S
320281	4-CN-PhCH ₂	3-F-PhCO	5-Cl-2-thienyl	O	C ₃₄ H ₂₆ ClFN ₆ O ₂ S
320282	4-CN-PhCH ₂	4-CN-PhCO	5-Cl-2-thienyl	O	C ₃₅ H ₂₆ ClN ₇ O ₂ S

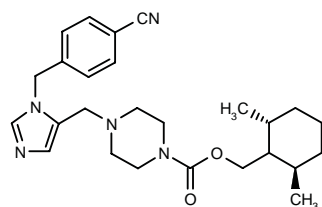
SOURCE – bioMerieux-Pierre Fabre.

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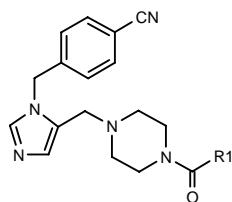
320303

4-[1-(4-Cyanobenzyl)-1*H*-imidazol-5-ylmethyl]piperazine-1-carboxylic acid 2(*R*),6(*R*)-dimethylcyclohexylmethyl ester



C26 H35 N5 O2; Mol wt: 449.5955

ACTION – An inhibitor of protein farnesyltransferase and protein geranylgeranyltransferase type I, potentially useful for the treatment of cancer, benign proliferative disorders, blindness related to retinal vascularization, hepatitis delta and related viral infections, postangioplasty restenosis and polycystic kidney disease. Other specifically claimed compounds are:



Compound	R1	Formula
320305	2(<i>R</i>),6(<i>S</i>)-(Me)2-cyclohexyl-CH ₂ O	C ₂₆ H ₃₅ N ₅ O ₂
320306	3,3,5,5-(Me)4-cyclohexyl-O	C ₂₇ H ₃₇ N ₅ O ₂
320307	3-[C(Me)2=CH]-2,2-(Me)2-cyclopropyl	C ₂₆ H ₃₃ N ₅ O
320308	3,3-(Me)2-cyclohexyl-O	C ₂₅ H ₃₃ N ₅ O ₂

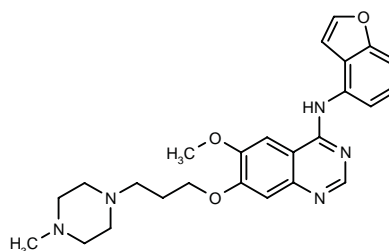
SOURCE – Merck & Co.

REFERENCES

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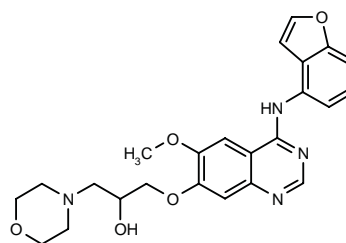
320429

N-(1-Benzofuran-4-yl)-6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinazolin-4-amine



C25 H29 N5 O3; Mol wt: 447.5361

ACTION – An inhibitor of nonreceptor tyrosine kinases, particularly the Src family of kinases, considered to have potential in the treatment of cancer. Another exemplified quinazoline derivative is:



320430: C24 H26 N4 O5

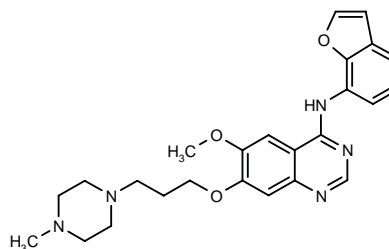
SOURCE – AstraZeneca.

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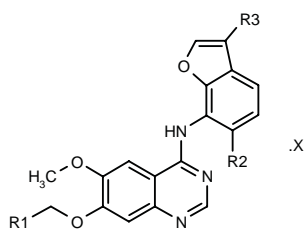
320432

N-(1-Benzofuran-7-yl)-6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinazolin-4-amine



C25 H29 N5 O3; Mol wt: 447.5361

ACTION – An inhibitor of nonreceptor tyrosine kinases, particularly the Src family of kinases, considered to have potential in the treatment of cancer. Other exemplified quinazoline derivatives are:



Compound	R1	R2	R3	X	Formula
320433	4-morpholinyl-CH ₂ CH ₂	Cl	H		C ₂₄ H ₂₅ ClN ₄ O ₄
320434	4-Me-1-Piz-CH ₂ CH ₂	Cl	Br		C ₂₅ H ₂₇ BrClN ₅ O ₃
320435	4-morpholinyl-CH ₂ CH(OH)	H	Cl	2HCl	C ₂₄ H ₂₅ ClN ₄ O ₅ ·2HCl
320436	4-Me-1-Piz	Cl	H		C ₂₃ H ₂₄ ClN ₅ O ₃
320437	1-pyrrolidinyl-CH ₂	Cl	H		C ₂₃ H ₂₃ ClN ₄ O ₃
320438	1-(t-BuOCO)-4-Pip-CH ₂	Cl	H		C ₂₉ H ₃₃ ClN ₄ O ₅
320439	4-Pip-CH ₂	Cl	H		C ₂₄ H ₂₅ ClN ₄ O ₃
320441	4-morpholinyl-CH ₂ CH ₂	Cl	Br		C ₂₄ H ₂₄ BrClN ₄ O ₄

SOURCE – AstraZeneca.

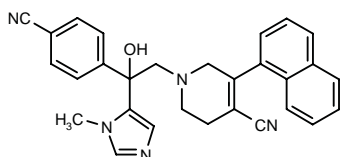
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A-345877

321013

1-[2-(4-Cyanophenyl)-2-hydroxy-2-(1-methyl-1*H*-imidazol-5-yl)ethyl]-5-(1-naphthyl)-1,2,3,6-tetrahydropyridine-4-carbonitrile



C₂₉ H₂₅ N₅ O; Mol wt: 459.5505

ACTION – Potent protein farnesyltransferase inhibitor (IC₅₀ = 0.45 nM) with high selectivity over geranylgeranyltransferase (IC₅₀ = 540 nM) and good cellular activity (IC₅₀ = 4 nM for inhibition of Ras protein farnesylation). It showed a good pharmacokinetic profile in dogs, with a half-life of 1.7 h and an oral bioavailability of 57%. Potentially useful for the treatment of cancer.

SOURCE – Abbott.

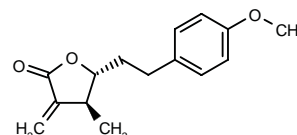
REFERENCES

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OTHER ONCOLYTIC DRUGS

319385

5(*R*)-[2-(4-Methoxyphenyl)ethyl]-4(*S*)-methyl-3-methylenetetrahydrofuran-2-one



C₁₅ H₁₈ O₃; Mol wt: 246.3042

ACTION – Antiproliferative agent able to induce apoptosis and to inhibit the growth of myeloid leukemia HL-60 cells with an IC₅₀ value of 4 μM. It also inhibited the proliferation induced by different mitogenic agents in murine splenocytes and human peripheral blood mononuclear cells, with no apparent toxic side effects.

SOURCES – Universidad de Alcalá, Alcalá de Henares (ES); Universidad del Bio-Bio, Chillán (CL); CSIC, Madrid (ES); Industrial Farmacéutica Cantabria; Universidad de Las Palmas de Gran Canaria, Las Palmas de Gran Canaria (ES).

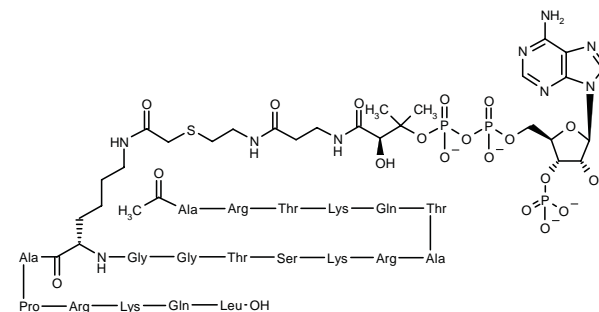
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2. González, A.G. et al. *Synthesis and antiproliferative activity of a new compound containing an α-methylene-γ-lactone group*. J Med Chem 2002, 45(12): 2358.

320494

N-Acetyl-L-alanyl-L-arginyl-L-threonyl-L-lysyl-L-glutaminyll-L-threonyl-L-alanyl-L-arginyl-L-lysyl-L-seryl-L-threonyl-glycyl-glycyl-*N*⁶-[2-[2-[*N*-[2(*R*)-hydroxy-3-[(hydroxy)-[(hydroxy)(3'-*O*-phosphoadenosine-5'-*O*-yl)phosphoryloxy]phosphoryloxy]-3-methylbutyryl]-β-alanyl-amino]ethyl-sulfanyl]acetyl]-L-lysyl-L-alanyl-L-prolyl-L-arginyl-L-lysyl-L-glutaminyll-L-leucine

H₃-CoA-20



C₁₁₅ H₁₉₉ N₄₂ O₄₅ P₃ S; Mol wt: 3015.0740

ACTION – A representative compound from a series of coenzyme A-peptide conjugates with the ability to inhibit histone acetyltransferase, and thus potentially useful for the treatment of cancer.

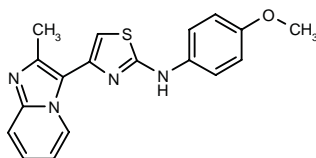
SOURCE – Rockefeller University, New York, NY (US).

REFERENCES

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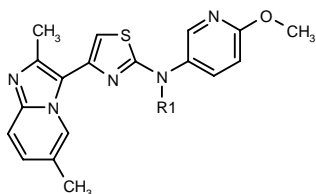
320524

N-(4-Methoxyphenyl)-4-(2-methylimidazo[1,2-*a*]pyridin-3-yl)thiazol-2-amine



C18 H16 N4 O S; Mol wt: 336.4174

ACTION – Antineoplastic agent reported to inhibit the proliferation of several cancer cell lines. Other exemplified imidazopyridine derivatives are:



Compound	R1	Formula
320525	H	C ₁₈ H ₁₇ N ₅ OS
320526	Ac	C ₂₀ H ₁₉ N ₅ O ₂ S

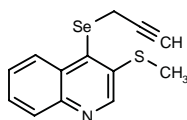
SOURCE – Sankyo.

REFERENCES

1. Hayakawa, I. et al. (Sankyo Co., Ltd.) *Imidazopyridine derivs*. WO 0234748.

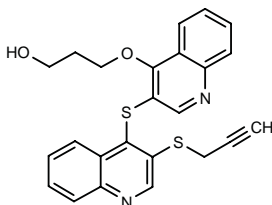
320809

3-(Methylsulfanyl)-4-(2-propynylselanyl)quinoline



C13 H11 N S Se; Mol wt: 292.2629

ACTION – Antiproliferative agent active against human breast carcinoma T-47D, human colon adenocarcinoma SW707 and human uroepithelial HCV29T cells (ID₅₀ = 1.8, 2.5 and 0.6 µg/ml, respectively). Another related propargyl thioquinoline is:



320808: C₂₄ H₂₀ N₂ O₂ S₂

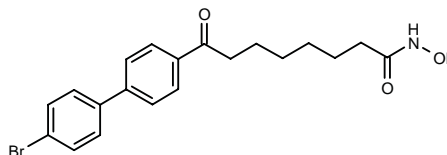
SOURCES – Medical University of Silesia, Katowice (PL); Polish Academy of Science, Kraków (PL).

REFERENCES

1. Boryczka, S. et al. *Synthesis and antiproliferative activity in vitro of new propargyl thioquinolines*. *Pharmazie* 2002, 57(3): 151.

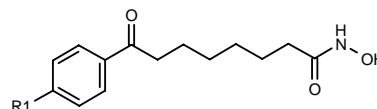
320867

8-(4'-Bromobiphenyl-4-yl)-8-oxooctanohydroxamic acid



C20 H22 Br N O3; Mol wt: 404.3018

ACTION – Potent histone deacetylase type 1 inhibitor (IC₅₀ = 2 nM) with strong antiproliferative activity against a panel of human cancer cells including breast carcinoma MDA-MB-231, non-small cell lung cancer A549, colon carcinoma HCT 116 and bladder carcinoma T24 cells (IC₅₀ = 0.05, 0.3, 0.87 and 0.8 nM, respectively). It induced p21 protein expression in T24 cells and both G₁ and G₂/M cell cycle arrest at concentrations of 5 µM or less. Other related compounds are:



Compound	R1	Formula
320868	Ph	C ₂₀ H ₂₃ NO ₃
320869	4-Ph-1-Piz	C ₂₄ H ₃₁ N ₃ O ₃

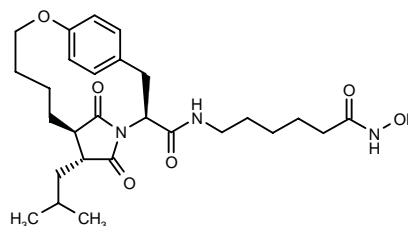
SOURCE – MethylGene.

REFERENCES

1. Delorme, D. et al. (MethylGene Inc.) *Inhibitors of histone deacetylase*. WO 0170675.
2. Woo, S.H. et al. *Structurally simple trichostatin A-like straight chain hydroxamates as potent histone deacetylase inhibitors*. *J Med Chem* 2002, 45(13): 2877.

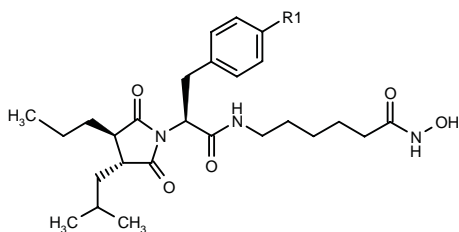
321097

(3*S*,6*R*,7*R*)-*N*-[5-(*N*-Hydroxycarbamoyl)pentyl]-6-isobutyl-5,18-dioxo-12-oxa-4-azatricyclo[11.2.2.1^{4,7}]octadeca-1(15),13,16-triene-3-carboxamide

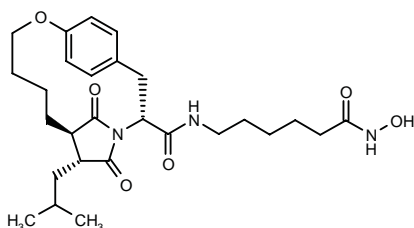


C27 H39 N3 O6; Mol wt: 501.6201

ACTION – Antineoplastic agent, a histone deacetylase inhibitor ($IC_{50} = 38$ nM) able to inhibit the proliferation of human fibrosarcoma HT-1080 and human breast cancer MDA-MB-435 cells ($IC_{50} = 0.25$ and 0.15 μ M, respectively). Other related succinimide hydroxamic acids are:



Compound	R1	Formula
321099	H	$C_{26}H_{39}N_3O_5$
321100	OMe	$C_{27}H_{41}N_3O_6$



321098: C27 H39 N3 O6

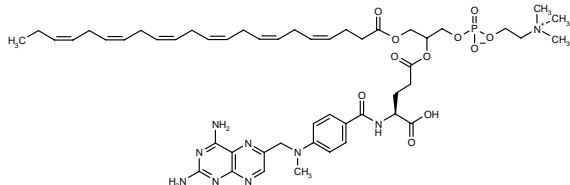
SOURCE – Abbott.

REFERENCES

1. Curtin, M.L. et al. *Succinimide hydroxamic acids as potent inhibitors of histone deacetylase (HDAC)*. 28th Natl Med Chem Symp (June 8-12, San Diego) 2002, Abst 68.

321426

2-*O*-[*N*-[4-[*N*-(2,4-Diaminopteridin-6-ylmethyl)-*N*-methylamino]benzoyl]-L-glutamyl]-3-*O*-[2-[(4*Z*,7*Z*,10*Z*,13*Z*,16*Z*,19*Z*)-docosa-4,7,10,13,16,19-hexaenoyloxy]-*sn*-glycero-3-*O*-phosphocholine inner salt



C50 H70 N9 O11 P; Mol wt: 1004.1290

ACTION – Antineoplastic agent, a phosphatidylcholine conjugated to docosahexaenoic acid and methotrexate reported to inhibit murine leukemia T27A cell proliferation.

SOURCES – Indiana University, Indianapolis, IN (US); Marshall University, Huntington, WV (US); Purdue University, West Lafayette, IN (US)

REFERENCES

1. Zerouga, M. et al. *Synthesis of a novel phosphatidylcholine conjugated to docosahexaenoic acid and methotrexate that inhibits cell proliferation*. *Anti-Cancer Drugs* 2002, 13(3): 301.

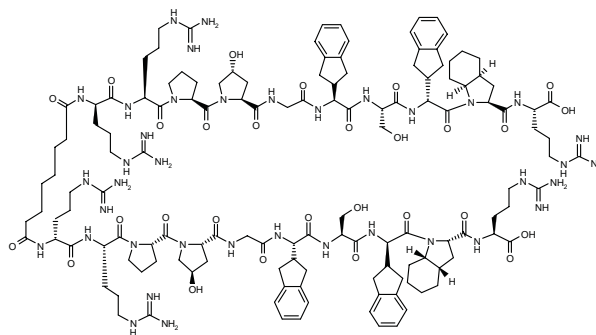
CU-201

292713

1,1'-(1,8-Dioxo-1,8-octanediyl)bis[D-arginyl-L-arginyl-L-prolyl-4(*R*)-hydroxy-L-prolyl-glycyl-2(*S*)-(2,3-dihydro-1*H*-inden-2-yl)glycyl-L-seryl-2(*R*)-(2,3-dihydro-1*H*-inden-2-yl)glycyl-(2*S*,3*aS*,7*aS*)-octahydro-1*H*-indol-2-ylcarbonyl-L-arginine

B-201

B-9870



C136 H200 N38 O28; Mol wt: 2815.3140

ACTION – Bradykinin antagonist dimer able to inhibit the growth of human small cell lung, non-small cell lung, prostate and breast cancer cells ($IC_{50} \sim 1-5$ μ M). Compound inhibited intracellular Ca^{2+} release in response to bradykinin ($IC_{50} = 10$ nM), activated c-Jun *N*-terminal kinase (JNK) and caspase 3, inhibited phospholipase C- β pathways and induced apoptosis. Potentially useful for the treatment of lung cancer.

SOURCES – University of Colorado, Boulder, CO (US); Eleanor Roosevelt Institute, Denver, CO (US); National Jewish Center, Denver, CO (US).

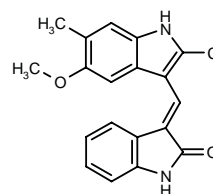
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2. Chan, D.C. et al. *Bradykinin antagonist dimer, CU201, inhibits the growth of human lung cancer cell lines in vitro and in vivo and produces synergistic growth inhibition in combination with other antitumor agents*. *Clin Cancer Res* 2002, 8(5): 1280.
3. Stewart, J.M. et al. *Bradykinin-related compounds as new drugs for cancer and inflammation*. *Can J Physiol Pharmacol* 2002, 80(4): 275.
4. Stewart, J.M. et al. *New class of drug candidates for lung and prostate cancer*. 220th ACS Natl Meet (Aug 20-24, Washington DC) 2000, Abst MEDI 1.

NSC-711616

319525

(*E*)-3-(2-Chloro-5-methoxy-6-methyl-1*H*-indol-3-ylmethylidene)-2,3-dihydro-1*H*-indol-2-one



C19 H15 Cl N2 O2; Mol wt: 338.7925

ACTION – Antineoplastic agent with good growth-inhibitory activity against a panel of human cancer cells (pIC = 6.7-7.2), where it was more active than vincristine. It may act as a tubulin-binding compound.

SOURCES – Università degli Studi di Bologna, Bologna (IT); Lithuanian Institute of Cardiology, Kaunas (LT).

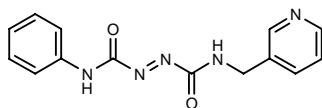
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RL-338

321139

*N*¹-Phenyl-*N*²-(pyridin-3-ylmethyl)diazene-1,2-dicarboxamide



C14 H13 N5 O2; Mol wt: 283.2897

ACTION – Cytotoxic agent able to significantly reduce survival of human cancer cell lines such as glioblastoma, cervical, laryngeal and mammary carcinomas including resistant cell lines. Compound was able to induce apoptosis in cervical carcinoma cells and this effect appeared to be due to a reduction in intracellular glutathione levels, rather than to a modification in *p53* and *BCL2* gene expression.

SOURCES – University of Ljubljana, Ljubljana (SI) Rudjer Boskovic Institute, Zagreb (HR).

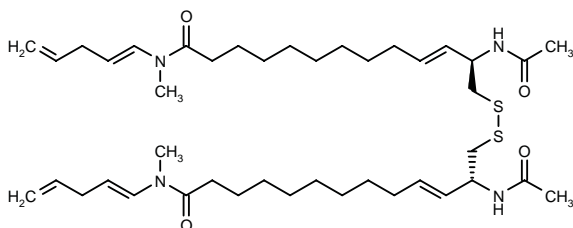
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1. Osmak, M. et al. *1-(3-Picolyl)-2-phenyldiazenedicarboxamide: A potential anticancer drug*. Rev Oncol 2002, 4(Suppl. 1): Abst 415.

SOMOCYSTINAMIDE A

320724

13,13'-Dithiobis[12(*R*)-acetamido-*N*-methyl-*N*-[1(*E*),4-pentadienyl]tridec-10(*E*)-enamide]



C42 H70 N4 O4 S2; Mol wt: 759.1710

ACTION – Cytotoxic agent extracted from a marine cyanobacteria assemblage (*Lyngbya majuscula*/ *Schizothrix* sp.) with strong cytotoxic activity against mouse neuroblastoma cells (IC₅₀ = 1.4 µg/ml).

SOURCE – Oregon State University, Corvallis, OR (US).

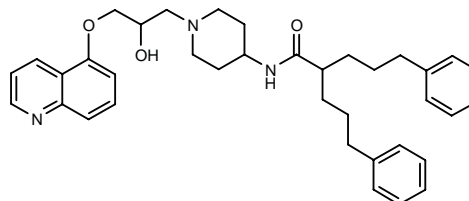
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MODULATORS OF THE THERAPEUTIC ACTIVITY OF ANTINEOPLASTIC AGENTS

320235

N-[1-[2-Hydroxy-3-(quinolin-5-yloxy)propyl]piperidin-4-yl]-5-phenyl-2-(3-phenylpropyl)pentanamide



C37 H45 N3 O3; Mol wt: 579.7805

ACTION – A representative compound from a series of piperidine derivatives able to modulate multidrug resistance through an interaction with the cellular transport proteins P-glycoprotein and MRP1.

SOURCE – Procter & Gamble.

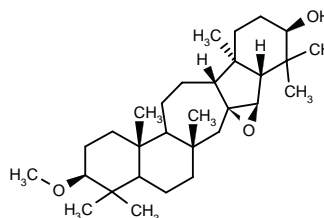
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1. Degenhardt, C.R. and Eickhoff, D.J. (The Procter & Gamble Co.) *Subst. six-membered heterocyclic cpds. useful for treating multidrug resistance and compns. and methods thereof*. US 6376514, WO 0232869.

CHEMOPREVENTIVE AGENTS

321318

(3*S*,6*aS*,7*aS*,8*aR*,8*bR*,10*R*,12*aS*,12*bR*,14*bR*)-3-Methoxy-4,4,6*a*,9,9,12*a*,14*b*-heptamethylperhydrobenzo[2,3]naphtho[1',2':6,7]azuleno[1,8*a-b*]oxiren-10-ol



C30 H50 O3; Mol wt: 458.7220

ACTION – Chemopreventive agent, a putative biosynthetic intermediate of jezananal A, a naturally occurring triterpene extracted from the stem bark of *Picea jezoensis* var. *jezoensis*. Compound displays strong inhibitory activity against Epstein-Barr virus early antigen activation induced by TPA in Raji cells; no toxicity was seen in these cells at pharmacologically active concentrations. In a mouse model of two-stage carcinogenesis induced by DMBA as initiator and TPA as promotor, compound reduced the percentage of papilloma-bearing mice to approximately 60% over 20 weeks.

SOURCES – Kinki University, Osaka (JP); Kyoto Prefectural University of Medicine, Kyoto (JP); Osaka University, Osaka (JP).

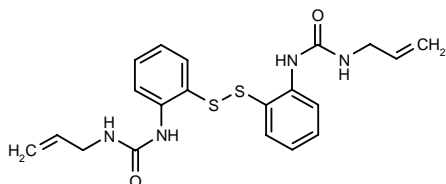
REFERENCES

1. Tanaka, R. et al. *Jezanals A and B: Two novel skeletal triterpene aldehydes from the stem bark of Picea jezoensis* var. *jezoensis*. *Tetrahedron* 2002, 58(13): 2505.

OCULAR MEDICATIONS

320925

3,3'-Dithiobis(1,2-phenylene)bis(1-allylurea)



C20 H22 N4 O2 S2; Mol wt: 414.5518

ACTION – A representative compound from a series of disulfide derivatives that act as mast cell stabilizers and may be useful for the treatment of allergic diseases. The compound was found to inhibit histamine release from human conjunctival mast cells in a model of allergic conjunctivitis.

SOURCE – Alcon.

REFERENCES

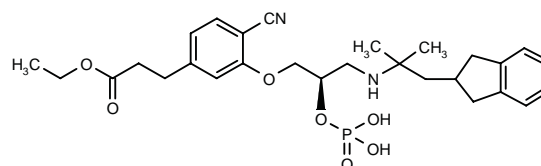
1. Feng, Z. et al. (Alcon Universal Ltd.) *Disulfide derivs. useful for treating allergic diseases*. US 2002058709.

METABOLIC DRUGS

TREATMENT OF BONE DISEASES

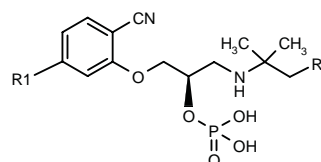
320055

3-[4-Cyano-3-[3-[2-(2,3-dihydro-1H-inden-2-yl)-1,1-dimethylethylamino]-2(R)-(phosphonoxy)propoxy]-phenyl]propionic acid ethyl ester



C28 H37 N2 O7 P; Mol wt: 544.5813

ACTION – Calcium antagonist, potentially useful for the treatment of osteoporosis and other disorders characterized by abnormal bone or mineral homeostasis such as osteosarcoma, periodontal disease, fracture healing, osteoarthritis, rheumatoid arthritis, Paget's disease and humoral hypercalcemia. Other specifically claimed compounds are:



Compound	R1	R2	Formula
320056	CH2CH2CO2H	2-indanyl	C ₂₆ H ₃₃ N ₂ O ₇ P
320059	4-CO2Et-Ph	5-Cl-2-thienyl	C ₂₇ H ₃₀ ClN ₂ O ₇ PS
320060	4-CO2H-Ph	5-Cl-2-thienyl	C ₂₆ H ₂₆ ClN ₂ O ₇ PS

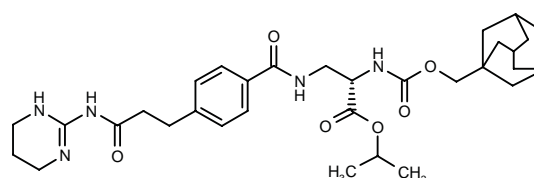
SOURCE – GlaxoSmithKline.

REFERENCES

1. Bhatnagar, P. et al. (GlaxoSmithKline Inc.) *Calcilytic cpds*. WO 0234204.

320257

2(S)-(Adamant-1-ylmethoxycarbonylamino)-3-[4-[2-[N-(1,4,5,6-tetrahydropyrimidin-2-yl)carbamoyl]ethyl]-benzamido]propionic acid isopropyl ester



C32 H45 N5 O6; Mol wt: 595.7365

ACTION – Chemopreventive agent, a putative biosynthetic intermediate of jezananal A, a naturally occurring triterpene extracted from the stem bark of *Picea jezoensis* var. *jezoensis*. Compound displays strong inhibitory activity against Epstein-Barr virus early antigen activation induced by TPA in Raji cells; no toxicity was seen in these cells at pharmacologically active concentrations. In a mouse model of two-stage carcinogenesis induced by DMBA as initiator and TPA as promotor, compound reduced the percentage of papilloma-bearing mice to approximately 60% over 20 weeks.

SOURCES – Kinki University, Osaka (JP); Kyoto Prefectural University of Medicine, Kyoto (JP); Osaka University, Osaka (JP).

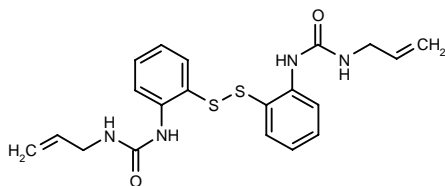
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OCULAR MEDICATIONS

320925

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SOURCE – Alcon.

REFERENCES

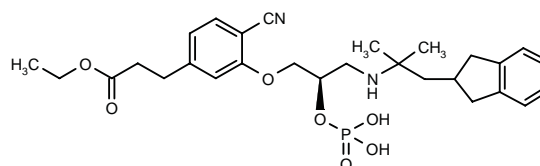
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METABOLIC DRUGS

TREATMENT OF BONE DISEASES

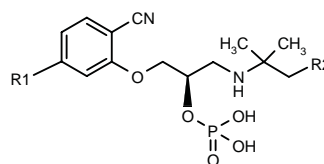
320055

3-[4-Cyano-3-[3-[2-(2,3-dihydro-1*H*-inden-2-yl)-1,1-dimethylethylamino]-2(*R*)-(phosphonoxy)propoxy]-phenyl]propionic acid ethyl ester



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ACTION – Calcium antagonist, potentially useful for the treatment of osteoporosis and other disorders characterized by abnormal bone or mineral homeostasis such as osteosarcoma, periodontal disease, fracture healing, osteoarthritis, rheumatoid arthritis, Paget's disease and humoral hypercalcemia. Other specifically claimed compounds are:



Compound	R1	R2	Formula
320056	CH ₂ CH ₂ CO ₂ H	2-indanyl	C ₂₆ H ₃₃ N ₂ O ₇ P
320059	4-CO ₂ Et-Ph	5-Cl-2-thienyl	C ₂₇ H ₃₀ ClN ₂ O ₇ PS
320060	4-CO ₂ H-Ph	5-Cl-2-thienyl	C ₂₅ H ₂₆ ClN ₂ O ₇ PS

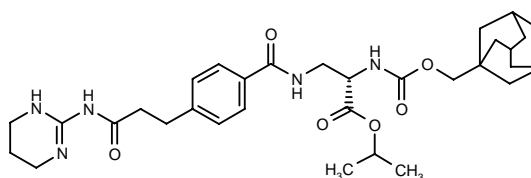
SOURCE – GlaxoSmithKline.

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320257

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SOURCES – Kinki University, Osaka (JP); Kyoto Prefectural University of Medicine, Kyoto (JP); Osaka University, Osaka (JP).

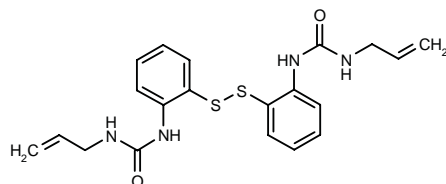
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OCULAR MEDICATIONS

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SOURCE – Alcon.

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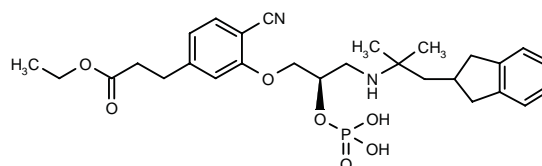
1. Feng, Z. et al. (Alcon Universal Ltd.) *Disulfide derivs. useful for treating allergic diseases*. US 2002058709.

METABOLIC DRUGS

TREATMENT OF BONE DISEASES

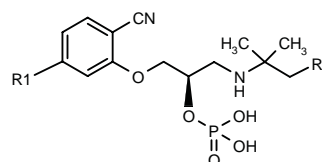
320055

3-[4-Cyano-3-[3-[2-(2,3-dihydro-1*H*-inden-2-yl)-1,1-dimethylethylamino]-2(*R*)-(phosphonooxy)propoxy]-phenyl]propionic acid ethyl ester



C28 H37 N2 O7 P; Mol wt: 544.5813

ACTION – Calcium antagonist, potentially useful for the treatment of osteoporosis and other disorders characterized by abnormal bone or mineral homeostasis such as osteosarcoma, periodontal disease, fracture healing, osteoarthritis, rheumatoid arthritis, Paget's disease and humoral hypercalcemia. Other specifically claimed compounds are:



Compound	R1	R2	Formula
320056	CH2CH2CO2H	2-indanyl	C ₂₈ H ₃₃ N ₂ O ₇ P
320059	4-CO2Et-Ph	5-Cl-2-thienyl	C ₂₇ H ₃₀ ClN ₂ O ₇ PS
320060	4-CO2H-Ph	5-Cl-2-thienyl	C ₂₆ H ₂₆ ClN ₂ O ₇ PS

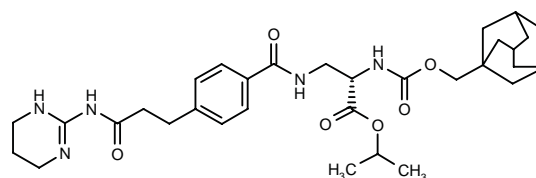
SOURCE – GlaxoSmithKline.

REFERENCES

1. Bhatnagar, P. et al. (GlaxoSmithKline Inc.) *Calcilytic cpds*. WO 0234204.

320257

2(*S*)-(Adamant-1-ylmethoxycarbonylamino)-3-[4-[2-[*N*-(1,4,5,6-tetrahydropyrimidin-2-yl)carbamoyl]ethyl]-benzamido]propionic acid isopropyl ester



C32 H45 N5 O6; Mol wt: 595.7365

ACTION – An $\alpha_v\beta_3$ (vitronectin) receptor antagonist with bone resorption-inhibitory activity in a rat model of parathyroid hormone-induced hypercalcemia at a dose of 30 mg/kg s.c. Potentially useful for the treatment of osteoporosis, cancer, inflammation, cardiovascular disorders, restenosis, arteriosclerosis, nephropathies, retinopathies and age-related macular degeneration.

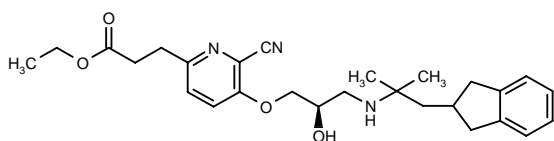
SOURCES – Aventis Pharma; Genentech.

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1. Peyman, A. et al. (Aventis Pharma Deutschland GmbH; Genentech, Inc.) (2S)-2-(Adamantan-1-ylmethoxycarbonylamino)-3-(4-(2-(1,4,5,6-tetrahydropyrimidin-2-ylcarbamoyl)ethyl)benzoylamino)propionic acid isopropyl ester, its preparation and its use. EP 1197488, WO 0230910.

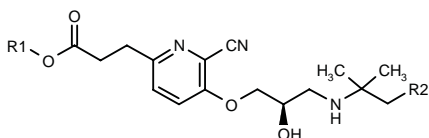
321057

3-[6-Cyano-5-[3-[2-(2,3-dihydro-1H-inden-2-yl)-1,1-dimethylethylamino]-2(R)-hydroxypropoxy]pyridin-2-yl]propionic acid ethyl ester



C27 H35 N3 O4; Mol wt: 465.5905

ACTION – Calcilytic compound expected to be useful for the treatment of bone or mineral disorders, particularly osteoporosis. Other specifically claimed compounds are:



Compound	R1	R2	Formula
321058	H	2-indanyl	C ₂₅ H ₃₁ N ₃ O ₄
321059	Et	4-MeO-Ph	C ₂₆ H ₃₃ N ₃ O ₅
321060	H	4-MeO-Ph	C ₂₃ H ₂₉ N ₃ O ₅
321062	Et	2-MeO-PhCH ₂ CH ₂	C ₂₇ H ₃₇ N ₃ O ₅
321063	H	2-MeO-PhCH ₂ CH ₂	C ₂₅ H ₃₃ N ₃ O ₅

SOURCE – GlaxoSmithKline.

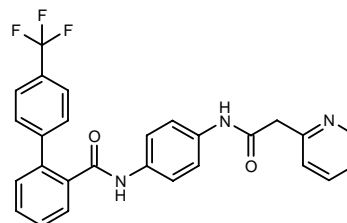
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TREATMENT OF LIPOPROTEIN DISORDERS

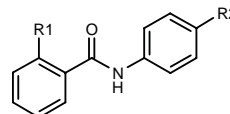
319788

N-[4-[2-(2-Pyridyl)acetamido]phenyl]-4'-(trifluoromethyl)-biphenyl-2-carboxamide



C27 H20 F3 N3 O2; Mol wt: 475.4680

ACTION – Apolipoprotein B (apo B) secretion inhibitor, as demonstrated in HepG2 cells by 92.2% inhibition at 1 μ M. Oral administration of this compound to ddY mice at 32 mg/kg decreased plasma levels of total cholesterol (17%) and triglycerides (64%). Potentially useful for the treatment of lipoprotein disorders such as hyperlipidemia, hyperlipoproteinemia, hypercholesterolemia, hypertriglyceridemia, atherosclerosis, pancreatitis, type 2 diabetes, obesity, coronary heart diseases, myocardial infarction, stroke, restenosis and syndrome X. Other exemplified benzamide compounds are:



Compound	R1	R2	Formula
319789	4-CF ₃ -Ph	2-Pyr-(CH ₂) ₃	C ₂₈ H ₂₃ F ₃ N ₂ O
319791	4-CF ₃ -Ph	6-NH ₂ -2-Pyr-(CH ₂) ₃	C ₂₈ H ₂₄ F ₃ N ₃ O
319794	3-CF ₃ -PhNH	2-Pyr-CH ₂ CH ₂ NH	C ₂₇ H ₂₃ F ₃ N ₄ O
319796	4-CF ₃ -Ph	2-Pyr-CH ₂ CH ₂ NH	C ₂₇ H ₂₂ F ₃ N ₃ O

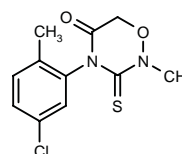
SOURCES – Daiso; Fujisawa.

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1. Takasugi, H. et al. (Daiso Co., Ltd.; Fujisawa Pharmaceutical Co., Ltd.) *Benzamide cpds. as Apo B secretion inhibitors.* WO 0228835.

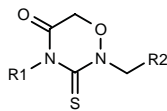
319917

4-(5-Chloro-2-methylphenyl)-2-methyl-3-thioxoperhydro-1,2,4-oxadiazin-5-one



C11 H11 Cl N2 O2 S; Mol wt: 270.7389

ACTION – Agent with the ability to elevate blood levels of HDL cholesterol, and thus potentially useful for the treatment of atherosclerotic conditions. This compound was shown to induce an increase of 236% in HDL cholesterol levels following oral administration to rats at a dose of 100 mg/kg/day. Other exemplified 3-thioxo-1,2,4-oxadiazin-5-one derivatives are:



Compound	R1	R2	Formula
319918	4-Cl-2-Me-Ph	H	C ₁₁ H ₁₁ ClN ₂ O ₂ S
319920	CH(Ph) ₂	H	C ₁₇ H ₁₆ N ₂ O ₂ S
319921	5-Cl-2-Me-Ph	Me	C ₁₂ H ₁₃ ClN ₂ O ₂ S
319922	5-indanyl	H	C ₁₃ H ₁₄ N ₂ O ₂ S
319923	2,5-(Me) ₂ -Ph	H	C ₁₂ H ₁₄ N ₂ O ₂ S
319924	2-Cl-6-Me-Ph	H	C ₁₁ H ₁₁ ClN ₂ O ₂ S
319925	2-i-Pr-Ph	H	C ₁₃ H ₁₆ N ₂ O ₂ S
319926	4-t-Bu-Ph	H	C ₁₄ H ₁₈ N ₂ O ₂ S
319927	4-PhO-Ph	H	C ₁₆ H ₁₄ N ₂ O ₃ S
319929	2-MeO-5-Cl-Ph	H	C ₁₁ H ₁₁ ClN ₂ O ₃ S

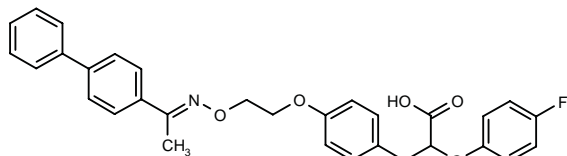
SOURCE – Wyeth.

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1. Elokda, H.M. and Sulkowski, T.S. (American Home Products Corp.) *3-Thioxo-1,2,4-oxadiazin-5-one and their use as anti-atherosclerotic agents*. US 2002061883, WO 0228845.

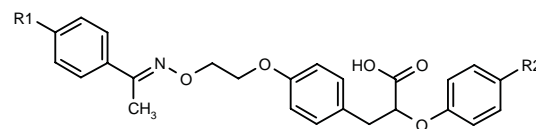
319976

3-[4-[2-[1-(4-Biphenyl)ethylideneaminoxy]ethoxy]phenyl]-2-(4-fluorophenoxy)propionic acid



C₃₁H₂₈F N O₅; Mol wt: 513.5622

ACTION – Agent with blood triglyceride-lowering activity (77% at 0.45 mg/kg/day p.o. for 1 week) and blood glucose-lowering activity (64% at 10 mg/kg/day p.o. for 3 days) in mice. Potentially useful for the treatment of hyperlipidemia, hyperglycemia, impaired glucose tolerance, hypertension, osteoporosis, pancreatitis, diabetic complications, arteriosclerosis, cataracts, gestational diabetes, polycystic ovary syndrome, inflammatory diseases, psoriasis, asthma, autoimmune diseases, etc. Other exemplified phenylpropionic acid derivatives are:



Compound	R1	R2	Formula
319977	4-F-Ph	F	C ₃₁ H ₂₇ F ₂ NO ₅
319978	2-Pyr	t-Bu	C ₃₄ H ₃₆ N ₂ O ₅
319979	2-Pyr	F	C ₃₀ H ₂₇ FN ₂ O ₅

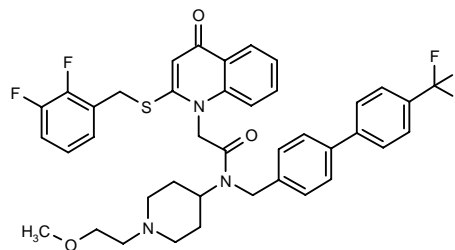
SOURCE – Sankyo.

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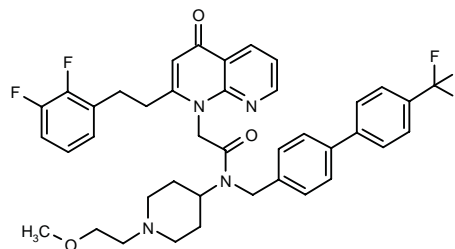
320250

2-[2-(2,3-Difluorobenzylsulfanyl)-4-oxo-1,4-dihydroquinolin-1-yl]-N-[1-(2-methoxyethyl)piperidin-4-yl]-N-[4'-(trifluoromethyl)biphenyl-4-ylmethyl]acetamide



C₄₀H₃₈F₅N₃O₃S; Mol wt: 735.8142

ACTION – Lipoprotein-associated phospholipase A₂ (Lp-PLA₂) inhibitor, potentially useful for the treatment of atherosclerosis. Another specifically claimed pyridinone derivative is:



320251: C₄₀H₃₉F₅N₄O₃

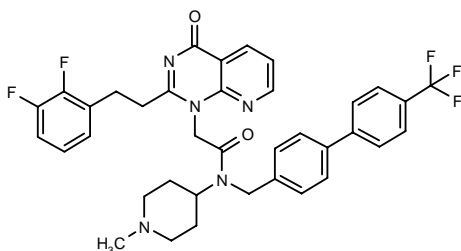
SOURCE – GlaxoSmithKline.

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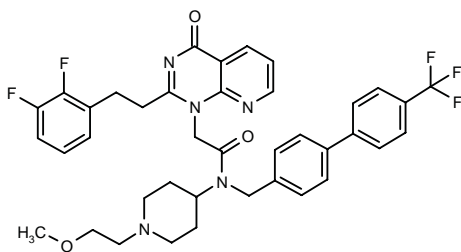
320252

2-[2-[2-(2,3-Difluorophenyl)ethyl]-4-oxo-1,4-dihydro-pyrido[2,3-*d*]pyrimidin-1-yl]-*N*-(1-methylpiperidin-4-yl)-*N*-[4'-(trifluoromethyl)biphenyl-4-ylmethyl]acetamide



C37 H34 F5 N5 O2; Mol wt: 675.6986

ACTION – Lipoprotein-associated phospholipase A₂ (Lp-PLA₂) inhibitor, potentially useful for the treatment of atherosclerosis. Another specifically claimed pyrimidinone derivative is:



320254: C39 H38 F5 N5 O3

SOURCE – GlaxoSmithKline.

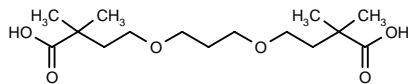
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1. Elliott, R.L. et al. (GlaxoSmithKline plc) *Pyrimidinone derivs. and their use in the treatment of atherosclerosis*. WO 0230911.

320311

2,2,12,12-Tetramethyl-5,9-dioxatridecanedioic acid

4,4'-(1,3-Propylene)bis(oxy)bis(2,2-dimethylbutyric acid)



C15 H28 O6; Mol wt: 304.3802

ACTION – Agent for the treatment of disorders of glucose and lipid metabolism including, but not limited to, cardiovascular diseases, dyslipidemia, dyslipoproteinemia, Alzheimer's disease, syndrome X, septicemia, thrombotic disorders, conditions mediated by PPAR (peroxisome proliferator-activated receptors), obesity, pancreatitis, hypertension, renal diseases, cancer, inflammation and impotence.

SOURCE – Esperion.

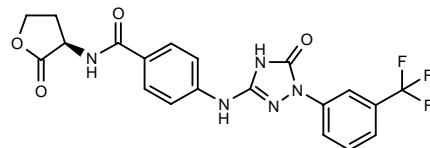
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TREATMENT OF OBESITY AND NUTRITIONAL DISORDERS

320246

N-[2-Oxotetrahydrofuran-3(*R*)-yl]-4-[5-oxo-1-[3-(trifluoromethyl)phenyl]-4,5-dihydro-1*H*-1,2,4-triazol-3-ylamino]benzamide



C20 H16 F3 N5 O4; Mol wt: 447.3714

ACTION – Agent with affinity for neuropeptide Y (NPY) receptors, considered to have potential in the treatment of obesity, bulimia, anorexia nervosa, diabetes, arterial hypertension, anxiety, depression, epilepsy, sexual dysfunction and sleep disorders.

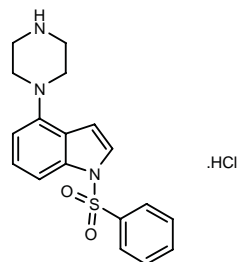
SOURCE – Servier.

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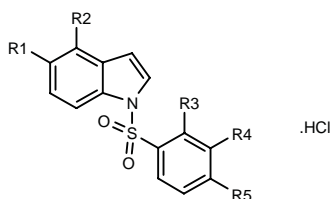
320611

1-(Phenylsulfonyl)-4-(1-piperazinyl)-1*H*-indole hydrochloride



C18 H19 N3 O2 S . HCl; Mol wt: 377.8940

ACTION – 5-HT₆ receptor antagonist, potentially useful for the treatment of obesity and CNS disorders including schizophrenia, Parkinson's disease, depression, attention deficit hyperactivity disorder and drug abuse. Other specifically claimed indoles include the following:



Compound	R1	R2	R3	R4	R5	Formula
320612	H	1-Piz	F	H	F	C ₁₈ H ₁₇ F ₂ N ₃ O ₂ S.HCl
320613	H	1-Piz	Me	Cl	H	C ₁₉ H ₂₀ ClN ₃ O ₂ S.HCl
320614	H	1-Piz	H	H	F	C ₁₈ H ₁₈ FN ₃ O ₂ S.HCl
320615	H	1-Piz	Me	H	H	C ₁₉ H ₂₁ N ₃ O ₂ S.HCl
320616	H	1-Piz	H	H	NO ₂	C ₁₈ H ₁₈ N ₄ O ₄ S.HCl
320617	H	1-Piz	H	CN	H	C ₁₉ H ₁₈ N ₄ O ₂ S.HCl
320618	4-Me-1-Piz	H	F	H	F	C ₁₉ H ₁₉ F ₂ N ₃ O ₂ S.HCl
320619	1-Piz	H	H	H	OBu	C ₂₂ H ₂₇ N ₃ O ₃ S.HCl

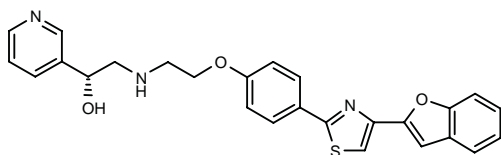
SOURCE – Biovitrum.

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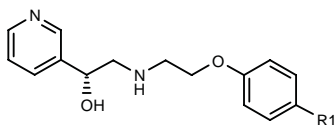
320663

2-[2-[4-[4-(1-Benzofuran-2-yl)thiazol-2-yl]phenoxy]ethyl-amino]-1(R)-(3-pyridyl)ethanol



C26 H23 N3 O3 S; Mol wt: 457.5517

ACTION – β_3 -Adrenoceptor agonist expected to be useful for the treatment of obesity, diabetes, irritable bowel syndrome, inflammatory bowel disease, esophagitis, duodenitis, Crohn's disease, proctitis, asthma, intestinal motility disorders, ulcer, gastritis, hypercholesterolemia, cardiovascular disease, urinary incontinence, depression, prostate disease, dyslipidemia and airways inflammatory disorders. Other specifically claimed 1-aryl-2-aminoethanol derivatives are:



Compound	R1	Formula
320664	2,5-(MeO)2-4-oxazolyl	C ₂₀ H ₂₃ N ₃ O ₃
320665	1-imidazolyl	C ₁₈ H ₂₀ N ₄ O ₂
320666	2-(MeOCH2)-4-oxazolyl	C ₂₀ H ₂₃ N ₃ O ₄
320667	2-Me-4-oxazolyl	C ₁₉ H ₂₁ N ₃ O ₃
320668	4-Me-2-thiazolyl	C ₁₉ H ₂₁ N ₃ O ₂ S
320669	4-oxazolyl	C ₁₈ H ₁₉ N ₃ O ₃
320670	2-(4-Pyr)-4-imidazolyl	C ₂₃ H ₂₃ N ₅ O ₂
320671	2-(2-thienyl)-4-thiazolyl	C ₂₂ H ₂₁ N ₃ O ₂ S ₂

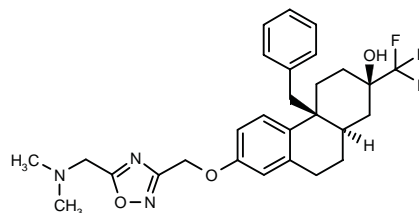
SOURCE – Pfizer.

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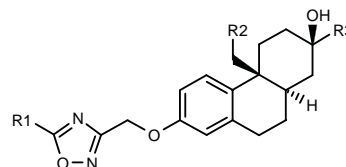
320684

(2R,4aS,10aR)-4a-Benzyl-7-[5-(dimethylaminomethyl)-1,2,4-oxadiazol-3-ylmethoxy]-2-(trifluoromethyl)-1,2,3,4,4a,9,10,10a-octahydrophenanthren-2-ol



C28 H32 F3 N3 O3; Mol wt: 515.5728

ACTION – A nonsteroidal glucocorticoid receptor modulator, particularly useful for the treatment of obesity, diabetes and inflammatory diseases. Other specifically claimed compounds include the following:



Compound	R1	R2	R3	Formula
320685	1-Pip-CH2	Ph	CF3	C ₃₁ H ₃₆ F ₃ N ₃ O ₃
320686	1-azetidiny-CH2CH2	Ph	Pr	C ₃₂ H ₄₁ N ₃ O ₃
320687	CH2CH2N(Me)2	Ph	Pr	C ₃₁ H ₄₁ N ₃ O ₃
320688	1-Me-3-Pip	Ph	CF3	C ₃₁ H ₃₆ F ₃ N ₃ O ₃
320689	CH2CH2N(Me)2	Ph	CF3	C ₂₉ H ₃₄ F ₃ N ₃ O ₃
320690	1-Me-3-Pip	Ph	1-propynyl	C ₃₃ H ₃₆ N ₃ O ₃
320691	CH2N(Me)2	Me	1-propynyl	C ₂₈ H ₃₃ N ₃ O ₃
320692	1-Pip-CH2	Me	1-propynyl	C ₂₈ H ₃₇ N ₃ O ₃

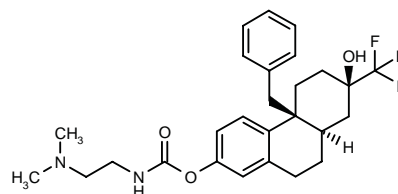
SOURCE – Pfizer.

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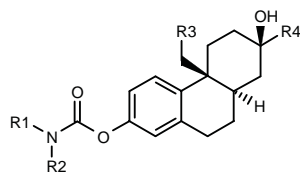
320693

N-[2-(Dimethylamino)ethyl]carbamic acid (4bS,7R,8aR)-4b-benzyl-7-hydroxy-7-(trifluoromethyl)-4b,5,6,7,8,8a,9,10-octahydrophenanthren-2-yl ester



C27 H33 F3 N2 O3; Mol wt: 490.5627

ACTION – A nonsteroidal glucocorticoid receptor modulator, particularly useful for the treatment of obesity, diabetes and inflammatory diseases. Other specifically claimed compounds include the following:



Compound	R1	R2	R3	R4	Formula
320694	CH ₂ CH ₂ N(Me) ₂	Me	Ph	Pr	C ₃₀ H ₄₂ N ₂ O ₃
320695	CH ₂ CH ₂ N(Me) ₂	Et	Ph	CF ₃	C ₂₉ H ₃₇ F ₃ N ₂ O ₃
320696	1-pyrrolidinyl-(CH ₂) ₃	H	Ph	CF ₃	C ₃₀ H ₃₇ F ₃ N ₂ O ₃
320697	1-Et-2-pyrrolidinyl-CH ₂	H	Ph	CF ₃	C ₃₀ H ₃₇ F ₃ N ₂ O ₃
320698	1-pyrrolidinyl-(CH ₂) ₃	H	Ph	Pr	C ₃₂ H ₄₄ N ₂ O ₃
320699	4-morpholinyl-CH ₂ CH ₂	H	Ph	CF ₃	C ₂₉ H ₃₅ F ₃ N ₂ O ₄
320700	2,2,6,6-(Me) ₄ -4-Pip	H	Ph	CF ₃	C ₃₂ H ₄₁ F ₃ N ₂ O ₃
320701	4-morpholinyl-(CH ₂) ₃	H	Me	1-propynyl	C ₂₇ H ₃₈ N ₂ O ₄

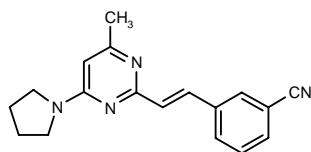
SOURCE – Pfizer.

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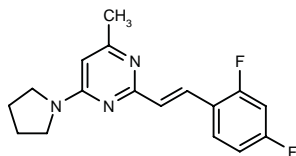
321053

3-[(*E*)-2-[4-Methyl-6-(1-pyrrolidinyl)pyrimidin-2-yl]vinyl]-benzonitrile



C₁₈ H₁₈ N₄; Mol wt: 290.3682

ACTION – Selective neuropeptide Y (NPY) Y₅ receptor antagonist (IC₅₀ = 18 nM), potentially useful for the treatment of arthritis, diabetes and, particularly, eating disorders and obesity. Another exemplified pyrimidine derivative is:



321055: C₁₇ H₁₇ F₂ N₃

SOURCE – Roche.

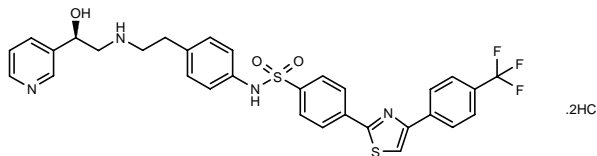
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L-796568*

292681

N-[4-[2-[2(*R*)-Hydroxy-2-(3-pyridyl)ethylamino]-ethyl]phenyl]-4-[4-(trifluoromethyl)phenyl]thiazol-2-yl]benzenesulfonamide dihydrochloride



C₃₁ H₂₇ F₃ N₄ O₃ S₂ . 2HCl; Mol wt: 697.6271

ACTION – High-affinity β₃-adrenoceptor agonist (EC₅₀ = 3.6 nM/l for increase in cAMP accumulation in CHO cells expressing the human receptor) with weak partial agonist activity at human β₁- and β₂-adrenoceptors. It displayed lipolytic and thermogenic activity in humans, significantly increasing energy expenditure at a dose of 1000 mg in a trial in 12 overweight to obese men, and increasing plasma glycerol and free fatty acid concentrations, while having no effect on heart rate, diastolic blood pressure, plasma catecholamines, potassium or leptin.

SOURCE – Merck & Co.

REFERENCES

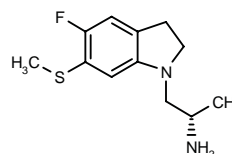
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6. van Baak, M.A. et al. *Acute thermogenic effect of L-796568, a novel β₃-adrenoceptor agonist, in obese men*. *Obes Res* 2000, 8(Suppl. 1): Abstr PB95.
7. Weber, A.E. *β₃ Adrenergic receptor agonists for the treatment of obesity*. 11th RSC-SCI Med Chem Symp (Sept 9-12, Cambridge) 2001, Abstr.

*Identified compound **292681** Drug Data Rep 2000, 022(11): 1044.

VER-5593

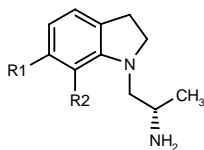
321123

1-[5-Fluoro-6-(methylsulfanyl)-2,3-dihydro-1*H*-indol-1-yl]propan-2(*S*)-amine



C₁₂ H₁₇ F N₂ S; Mol wt: 240.3443

ACTION – Potent and selective 5-HT_{2C} receptor agonist with nanomolar affinity for 5-HT_{2C} receptors ($K_i = 3$ nM) and high selectivity over 5-HT_{2B} and 5-HT_{2A} receptors ($K_i = 21$ and 53 nM, respectively). In food-deprived rats, compound dose-dependently reduced food intake following oral administration. Potentially useful for the treatment of obesity. Other related indolines are:



Compound	R1	R2	Formula
VER-3323 [321125]	Br	H	C ₁₁ H ₁₅ BrN ₂
VER-5384 [321126]	-OCH ₂ CH ₂ -		C ₁₃ H ₁₈ N ₂ O

SOURCE – Vernalis Research.

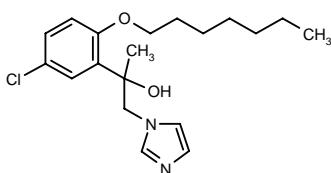
REFERENCES

1. Adams, D.R. et al. (Vernalis Research Ltd.) *Indoline derivs. as 5-HT_{2B} and/or 5-HT_{2C} receptor ligands*. EP 1109784, US 6380238, WO 0012475.
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HEMATINIC AGENTS AND HEMATOPOIETIC GROWTH FACTORS

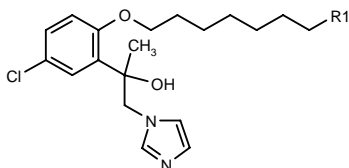
319969

2-[5-Chloro-2-(heptyloxy)phenyl]-1-(1*H*-imidazol-1-yl)propan-2-ol



C₁₉ H₂₇ Cl N₂ O₂; Mol wt: 350.8873

ACTION – Agent with granulocyte colony-stimulating factor (G-CSF)-like activity for use in the treatment of neutropenia. The compound was shown to induce the proliferation of G-CSF-dependent cells *in vitro*. Other exemplified imidazole derivatives are:



Compound	R1	Formula
319970	Et	C ₂₁ H ₃₁ ClN ₂ O ₂
319971	Me	C ₂₀ H ₂₉ ClN ₂ O ₂

SOURCE – SSP.

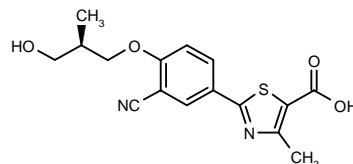
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TREATMENT OF DISORDERS OF PURINE AND PYRIMIDINE METABOLISM

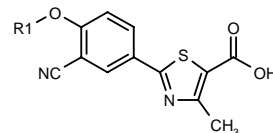
320333

2-[3-Cyano-4-[3-hydroxy-2(*R*)-methylpropoxy]phenyl]-4-methylthiazole-5-carboxylic acid



C₁₆ H₁₆ N₂ O₄ S; Mol wt: 332.3784

ACTION – Xanthine oxidase inhibitor ($K_i = 0.7$ nM), potentially useful for the treatment of gout, hyperuricemia and diseases associated with organ ischemia-reperfusion injury. Other exemplified 2-phenylthiazole derivatives include the following:



Compound	R1	Formula
320334	CH ₂ C(Me)2OH	C ₁₆ H ₁₆ N ₂ O ₄ S
320336	H	C ₁₂ H ₈ N ₂ O ₃ S
320337	CH ₂ CH(Me)CO ₂ H	C ₁₆ H ₁₄ N ₂ O ₅ S
320425	(S)-CH ₂ CH(Me)CH ₂ OH	C ₁₆ H ₁₆ N ₂ O ₄ S

SOURCE – Teijin.

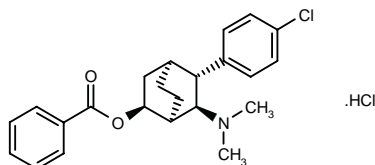
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TREATMENT OF POISONING AND DRUG DEPENDENCY

319262

Benzoic acid (1*S**,2*S**,4*S**,5*R**,6*R**)-5-(4-chlorophenyl)-6-(dimethylamino)bicyclo[2.2.2]oct-2-yl ester hydrochloride



C23 H26 Cl N O2 . HCl; Mol wt: 420.3773

ACTION – Dopamine transporter inhibitor ($IC_{50} = 33.5$ nM) with 340-fold selectivity over the 5-HT transporter and an IC_{50} value of 0.137 μ M for inhibition of dopamine uptake. Potentially useful for the treatment of cocaine abuse.

SOURCES – Emory University, Atlanta, GA (US); Georgia Institute of Technology, Atlanta, GA (US); Mercer University, Atlanta, GA (US).

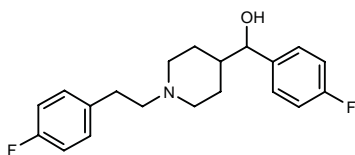
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1. Coons, S. et al. *Synthesis and pharmacology of potential site-specific cocaine abuse treatment agents: The role of the phenyl group in 2-substituted-6-aminobicyclo[2.2.2]octanes*. *Med Chem Res* 2002, 11(1): 24.

DIAGNOSTIC AGENTS

319684

1-(4-Fluorophenyl)-1-[1-[2-(4-fluorophenyl)ethyl]piperidin-4-yl]methanol



C20 H23 F2 N O; Mol wt: 331.4037

ACTION – High-affinity ligand for 5-HT_{2A} receptors ($K_i = 1.63$ nM) with high selectivity over other 5-HT receptors ($IC_{50} = 503, 1345$ and $> 10,000$ nM against 5-HT_{2C}, 5-HT₇ and 5-HT₆, respectively), dopamine D2 receptors ($K_i > 10,000$ nM) and α_1 - and α_2 -adrenoceptors ($K_i = 303$ and 1032 nM, respectively). Compared to the selective 5-HT_{2A} ligand altanserin, it was approximately 300-fold more selective for 5-HT_{2A} receptors. Potentially useful as a 5-HT_{2A} ligand for PET (positron emission tomography) and SPECT (single photon emission computed tomography) brain imaging.

SOURCES – Harvard Medical School, Boston, MA (US); Massachusetts General Hospital, Boston, MA (US); Yale University, New Haven, CT (US).

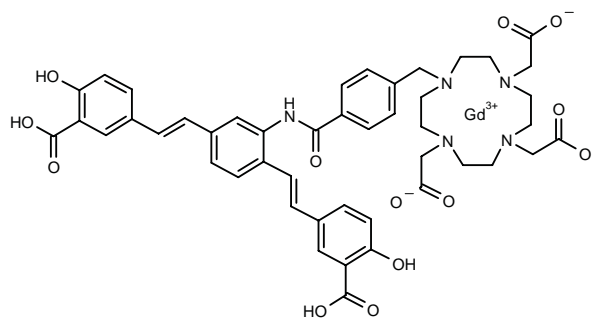
REFERENCES

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BSB-GdDO3A

320450

[10-[4-[N-[2,5-Bis[2-(3-carboxyl-4-hydroxyphenyl)vinyl]phenyl]carbamoyl]benzyl]-1,4,7,10-tetrazacyclododecan-1,4,7-tris(acetato)(3-)]gadolinium



C46 H46 Gd N5 O13; Mol wt: 1034.1410

ACTION – Gadolinium complex containing an amyloid-binding moiety for use as a magnetic resonance imaging agent in the diagnosis of Alzheimer's disease.

SOURCE – California Institute of Technology, Pasadena, CA (US).

REFERENCES

1. (California Institute of Technology) *Magnetic resonance imaging agents for in vivo labeling and detection of amyloid deposits*. WO 0228441.

PERFLEXANE LIPID MICROSPHERES

228512

Perfluorohexane-based ultrasound contrast agent that utilizes injectable-grade components to create dry, hollow, sterilized spheres that are reconstituted with water to form microscopic bubbles

AFO150

AF-0145

AF-145

Imavist (former brand name)

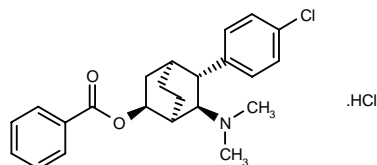
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INDICATION – Contrast enhancement during ultrasound imaging to opacify the left ventricle and thereby improve visualization of the main pumping chamber of the heart and to improve delineation of the endocardial borders of the heart.

TREATMENT OF POISONING AND DRUG DEPENDENCY

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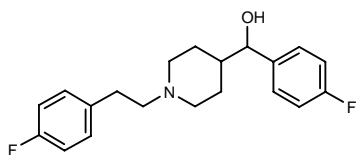
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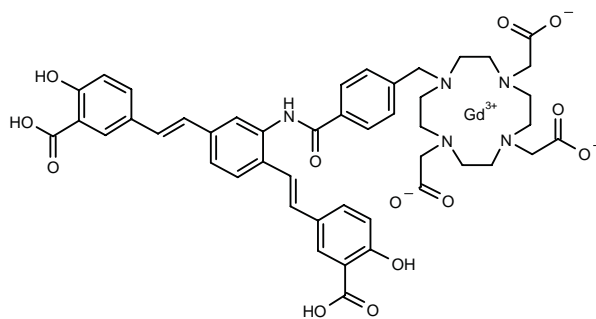
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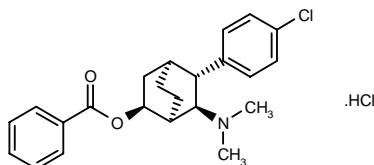
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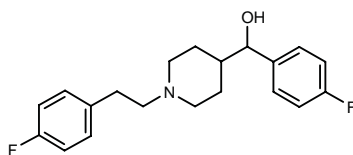
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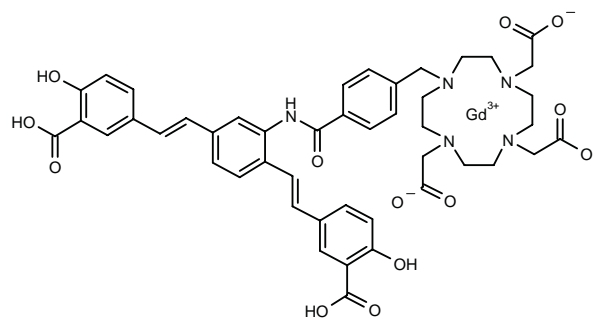
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320450

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SOURCE – California Institute of Technology, Pasadena, CA (US).

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AF-0145

AF-145

Imavist (former brand name)

ACTION – Perfluorohexane-based ultrasound contrast agent.

INDICATION – Contrast enhancement during ultrasound imaging to opacify the left ventricle and thereby improve visualization of the main pumping chamber of the heart and to improve delineation of the endocardial borders of the heart.

PRESENTATION – Vials containing 200 mg *Imagent*® powder for injectable suspension. Each vial of powder contains: 9.2 mg 1,2-dimyristoyl-*sn*-glycero-3-phosphocholine (DMPC), 75 mg hydroxyethyl starch, 2.1 mg poloxamer 188, 75 mg sodium chloride and 36 mg sodium phosphate buffer in a vial filled with a mixture of 17% v/v perflhexane vapor in nitrogen.

PROPRIETARY NAME – *Imagent* (US).

SOURCE – Alliance.

REFERENCES

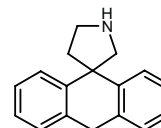
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21. *Ultrasound contrast agent deemed approvable by the FDA*. *DailyDrugNews.com* (Daily Essentials) 2000, Aug 24.

PHARMACOLOGICAL TOOLS

SpAMDA

320993

10*H*-Spiro[anthracene-9,3'-pyrrolidine]



C17 H17 N; Mol wt: 235.3283

ACTION – High-affinity 5-HT_{2A} receptor ligand ($K_i = 4$ nM) with functional antagonist activity.

SOURCE – Virginia Commonwealth University, Richmond, VA (US).

REFERENCES

1. Peddi, S. et al. *Receptor model-based design & synthesis of novel 5-HT_{2A} receptor ligands*. 28th Natl Med Chem Symp (June 8-12, San Diego) 2002, Abst 16.

PRESENTATION – Vials containing 200 mg *Imagent*[®] powder for injectable suspension. Each vial of powder contains: 9.2 mg 1,2-dimyristoyl-*sn*-glycero-3-phosphocholine (DMPC), 75 mg hydroxyethyl starch, 2.1 mg poloxamer 188, 75 mg sodium chloride and 36 mg sodium phosphate buffer in a vial filled with a mixture of 17% v/v perflhexane vapor in nitrogen.

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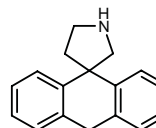
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20. *Study using Imavist for improved detection of prostate cancer set to begin*. *DailyDrugNews.com* (Daily Essentials) 2001, Oct 11.
21. *Ultrasound contrast agent deemed approvable by the FDA*. *DailyDrugNews.com* (Daily Essentials) 2000, Aug 24.

PHARMACOLOGICAL TOOLS

SpAMDA

320993

10*H*-Spiro[anthracene-9,3'-pyrrolidine]



C17 H17 N; Mol wt: 235.3283

ACTION – High-affinity 5-HT_{2A} receptor ligand ($K_i = 4$ nM) with functional antagonist activity.

SOURCE – Virginia Commonwealth University, Richmond, VA (US).

REFERENCES

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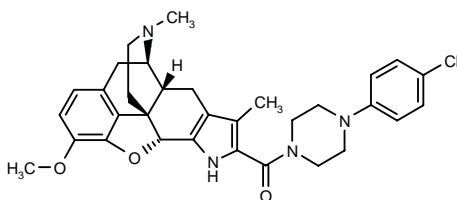
ANALGESIC AND ANESTHETIC DRUGS

ANALGESIC DRUGS

320384

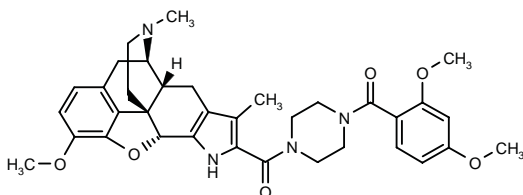
1-[4-(4-Chlorophenyl)piperazin-1-yl]-1-[(4b*S*,8*R*,8a*R*,12b*R*)-1-methoxy-7,10-dimethyl-5,6,7,8,8a,9,12,12b-octahydro-4,8-methano[1]benzofuro[3,2-*e*]pyrrolo[2,3-*g*]-isoquinolin-11-yl]methanone

5'-[4-(4-Chlorophenyl)piperazin-1-ylcarbonyl]-4,5-epoxy-3-methoxy-4',17-dimethylpyrrolo[2',3':6,7]morphinan



C32 H35 Cl N4 O3; Mol wt: 559.1065

ACTION – Agent with affinity for delta opioid receptors and potential as an analgesic agent, and also in the treatment of transplant rejection, allergy, inflammation, drug and alcohol abuse, neurodegenerative disorders, cardiovascular and respiratory diseases, cough, mental illness, epilepsy and gastrointestinal disorders such as gastritis, diarrhea and irritable bowel syndrome. Another exemplified morphinoid derivative is:



320385: C35 H40 N4 O6

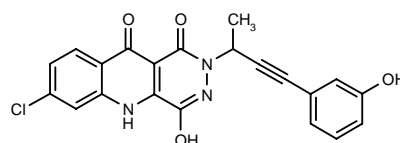
SOURCE – GlaxoSmithKline.

REFERENCES

1. Dondio, G. et al. (GlaxoSmithKline SpA) *Morphinoid derivs. as δ -opioid agonists and antagonists*. WO 0230935.

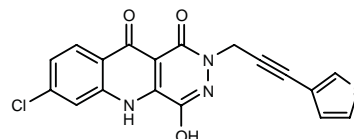
321236

7-Chloro-4-hydroxy-2-[3-(3-hydroxyphenyl)-1-methyl-2-propynyl]pyridazino[4,5-*b*]quinoline-1,10(2*H*,5*H*)-dione



C21 H14 Cl N3 O4; Mol wt: 407.8116

ACTION – Orally active glycine antagonist with nanomolar *in vitro* binding affinity for the glycine B site of the NMDA receptor (K_i = 5.9 nM). Potentially useful as an analgesic agent. Another related compound is:



321506: C18 H10 Cl N3 O3 S

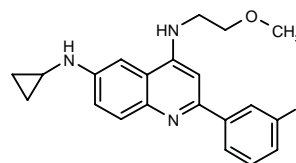
SOURCE – AstraZeneca.

REFERENCES

1. Horchler, C.L. et al. *Synthesis of 7-chloro-4-hydroxy-2-(3-(aryl/heteroaryl)prop-2-ynyl)1,2,5,10-tetrahydropyridazino[4,5-*b*]quinoline-1,10-diones (PQD I); potent oral glycine antagonists*. 28th Natl Med Chem Symp (June 8-12, San Diego) 2002, Abst 19.

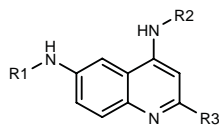
321295

*N*⁶-Cyclopropyl-2-(3-fluorophenyl)-*N*⁴-(2-methoxyethyl)quinoline-4,6-diamine



C21 H22 F N3 O; Mol wt: 351.4228

ACTION – N-Type calcium channel antagonist with an IC_{50} of 1.75 μ M against N-type calcium channels in IMR32 cells. Potentially useful as an analgesic agent. Other exemplified compounds are:



Compound	R1	R2	R3	Formula
321296	H	Pr	Ph	C ₁₈ H ₁₉ N ₃
321297	H	H	C5H11	C ₁₄ H ₁₉ N ₃
321298	cyclopropyl	Me	3-F-Ph	C ₁₉ H ₁₈ FN ₃

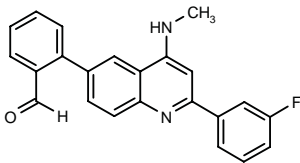
SOURCE – AstraZeneca.

REFERENCES

1. Chapdelaine, M. et al. (AstraZeneca AB) *N-Type calcium channel antagonists for the treatment of pain.* WO 0236567.

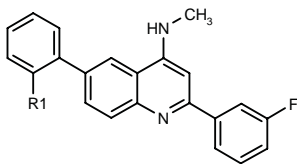
321299

2-[2-(3-Fluorophenyl)-4-(methyamino)quinolin-6-yl]-benzaldehyde



C23 H17 F N2 O; Mol wt: 356.3983

ACTION – N-Type calcium channel antagonist with an IC₅₀ of 5.38 μM against N-type calcium channels in IMR32 cells. Potentially useful as an analgesic agent. Other exemplified compounds are:



Compound	R1	Formula
321300	Cl	C ₂₂ H ₁₆ ClFN ₂
321301	H	C ₂₂ H ₁₇ FN ₂
321302	Me	C ₂₃ H ₁₉ FN ₂
321303	OMe	C ₂₃ H ₁₉ FN ₂ O

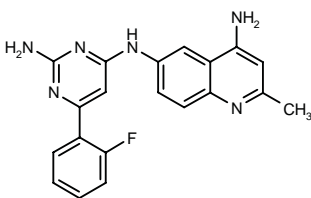
SOURCE – AstraZeneca.

REFERENCES

1. Chapdelaine, M. et al. (AstraZeneca AB) *N-Type calcium channel antagonists for the treatment of pain.* WO 0236569.

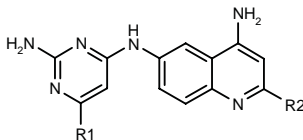
321304

N⁶-[2-Amino-6-(2-fluorophenyl)pyrimidin-4-yl]-2-methyl-quinoline-4,6-diamine



C20 H17 F N6; Mol wt: 360.3943

ACTION – N-Type calcium channel antagonist with an IC₅₀ of 2.37 μM against N-type calcium channels in IMR32 cells. Potentially useful as an analgesic agent. Other exemplified compounds are:



Compound	R1	R2	Formula
321305	CF3	Ph	C ₂₀ H ₁₅ F ₃ N ₆
321306	3-F-Ph	Me	C ₂₀ H ₁₇ FN ₆
321307	2-MeO-Ph	Ph	C ₂₆ H ₂₂ N ₆ O

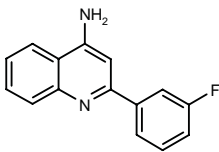
SOURCE – AstraZeneca.

REFERENCES

1. Chaudhari, B. et al. (AstraZeneca AB) *N-Type calcium channel antagonists for the treatment of pain.* WO 0236586.

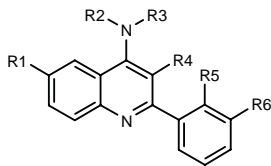
321308

2-(3-Fluorophenyl)quinolin-4-amine



C15 H11 F N2; Mol wt: 238.2639

ACTION – N-Type calcium channel antagonist with an IC₅₀ of 2.1 μM against N-type calcium channels in IMR32 cells. *In vivo*, compound was effective in reducing licking in the formalin pain test when administered to rats at 30 mg/kg i.p. or p.o. (93 and 41% inhibition, respectively). Potentially useful as an analgesic agent. Other exemplified compounds are:



Compound	R1	R2	R3	R4	R5	R6	Formula
321309	NH2	H	H	H	H	H	C ₁₅ H ₁₃ N ₃
321310	H	H	H	H	H	H	C ₁₅ H ₁₂ N ₂
321311	H	Me	H	H	H	F	C ₁₆ H ₁₃ FN ₂
321312	H	Me	Me	H	H	F	C ₁₇ H ₁₅ FN ₂
321313	H	H	H	Me	H	H	C ₁₆ H ₁₄ N ₂
321314	H	H	H	-(CH2)2-	H	H	C ₁₇ H ₁₄ N ₂
321315	H	H	H	H	H	Me	C ₁₆ H ₁₄ N ₂

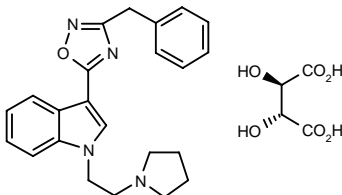
SOURCE – AstraZeneca.

REFERENCES

1. Ernst, G. et al. (AstraZeneca AB) *N-Type calcium channel antagonists for the treatment of pain.* WO 0236568.

321325

3-(3-Benzyl-1,2,4-oxadiazol-5-yl)-1-[2-(1-pyrrolidinyl)-ethyl]-1*H*-indole tartrate



C23 H24 N4 O . C4 H6 O6; Mol wt: 522.5550

ACTION – Analgesic agent, a representative compound from a series of 3-(1,2,4-oxadiazol-5-yl)-1*H*-indole derivatives with the ability to modulate cannabinoid receptors; compound gave IC₅₀ values of 0.05 and 1.6 μM, respectively, against CB₁ and CB₂ receptors in binding assays. It demonstrated analgesic activity in the rat tail-flick test and in a rat model of neuropathic pain.

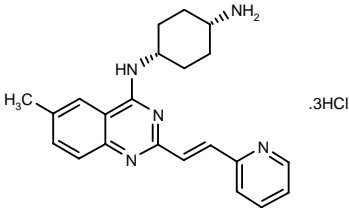
SOURCE – Amrad.

REFERENCES

1. Moloney, P.G. and Robertson, A.D. (Amrad Corp.) *3-Oxadiazol-5-yl-1-aminoalkyl-1*H*-indole derivs.* WO 0236590.

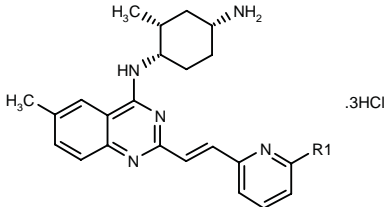
321488

cis-*N*-[6-Methyl-2-[2-(2-pyridyl)vinyl]quinazolin-4-yl]-cyclohexane-1,4-diamine trihydrochloride



C22 H25 N5 . 3HCl; Mol wt: 468.8572

ACTION – Nociceptin (N/OFQ) receptor ligand with analgesic activity, giving a K_i value of 0.018 μM at nociceptin receptors in binding assays and exhibiting 16-fold selectivity over mu opioid receptors. It demonstrated *in vivo* analgesic activity in the mouse formalin test. Potentially useful for the treatment of pain, migraine, chronic rheumatism, neuralgia, morphine resistance and allodynia associated with zoster virus infection. Other exemplified quinazoline derivatives are:



Compound	R1	Formula
321489	H	C23H27N5.3HCl
321490	Me	C24H29N5.3HCl

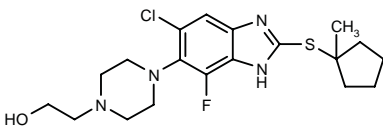
SOURCE – Nippon Shinyaku.

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1. Okano, M. and Mori, K. (Nippon Shinyaku Co., Ltd.) *Quinazoline derivs. and drugs.* WO 0236577.

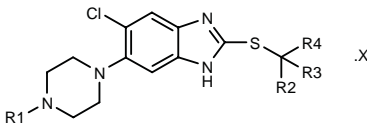
321923

2-[4-[5-Chloro-7-fluoro-2-(1-methylcyclopentylsulfanyl)-1*H*-benzimidazol-6-yl]piperazin-1-yl]ethanol



C19 H26 Cl F N4 O S; Mol wt: 412.9584

ACTION – An antagonist of ORL1 (nociceptin, N/OFQ) receptors that gave an IC₅₀ of 0.95 nM against ORL1 receptors expressed in CHO cells and antagonized nociceptin-induced activation of ORL1 receptors with an IC₅₀ of 0.57 nM. Potentially useful as an analgesic agent, as well as for the treatment of migraine, gout, rheumatism, morphine resistance, Alzheimer’s disease, dementia, schizophrenia, Parkinson’s disease, depression, diabetes insipidus, polyuria and hypotension. Other exemplified benzimidazole derivatives include the following:



Compound	R1	R2	R3	R4	X	Formula
321924	H	H	Et	Et	2HCl	C ₁₆ H ₂₃ ClN ₄ S .2HCl
321925	H	H	Me	t-BuCH2	2HCl	C ₁₈ H ₂₇ ClN ₄ S .2HCl
321926	CH2CH2OH	H	Et	Et	2HCl	C ₁₈ H ₂₇ ClN ₄ OS .2HCl
321927	CH2CH2OH	Me	Me	4-morpholinyl-CH2	3HCl	C ₂₁ H ₃₂ ClN ₅ O ₂ S .3HCl
321929	cyclopropyl-CH2	H	H	cyclohexyl		C ₂₂ H ₃₁ ClN ₄ S

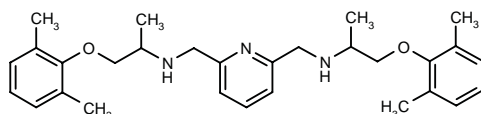
SOURCE – Banyu.

REFERENCES

1. Okamoto, O. et al. (Banyu Pharmaceutical Co., Ltd.) *Benzimidazole derivs.* WO 0240019.

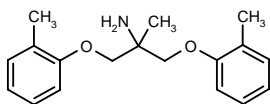
322321

N,N'-(Pyridin-2,6-diyl)bis(methylene)bis[1-(2,6-dimethylphenoxy)propan-2-amine]



C29 H39 N3 O2; Mol wt: 461.6461

ACTION – Analgesic agent, a mexiletine homodimer with over 10-fold higher affinity for voltage-gated Na⁺ channels compared to the parent compound. *In vivo*, compound inhibited carrageenan-induced thermal hyperalgesia with an ED₅₀ value of 3 mg/kg i.p., compared to a value of 47 mg/kg i.p. for mexiletine; it was also effective against tactile allodynia in spinal nerve-ligated animals with an ED₅₀ value of 6 mg/kg i.p., whereas mexiletine at 30 mg/kg i.p. had no effect. Another related compound is:



321944: C18 H23 N O2

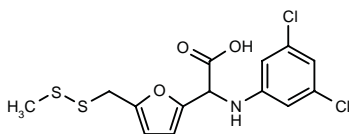
SOURCES – Advanced Medicine; Deltagen.

REFERENCES

1. Armstrong, S.R. et al. *In vitro and in vivo characterization of mexiletine homodimers.* Pharmacologist 2002, 44(2, Suppl. 1): Abst 37.14.

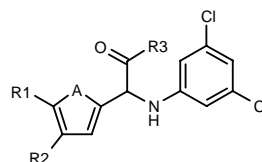
322355

2-(3,5-Dichlorophenylamino)-2-[5-(methylsulfonylmethyl)furan-2-yl]acetic acid



C14 H13 Cl2 N O3 S2; Mol wt: 378.2987

ACTION – Agent with affinity for the glycine site of NMDA receptors (K_i = 0.290 μM in rat brain homogenates) and potential as an analgesic agent. Other exemplified compounds include the following:



Compound	R1	R2	R3	A	Formula
322357	CH2SMe	H	ONa	O	C ₁₄ H ₁₂ Cl ₂ NNaO ₃ S
322358	CH2SAc	H	OH	O	C ₁₅ H ₁₃ Cl ₂ NO ₄ S
322359	2-furyl-CH2SSCH2	H	OH	O	C ₁₈ H ₁₅ Cl ₂ NO ₄ S ₂
322360	CH2OAc	H	OH	O	C ₁₅ H ₁₃ Cl ₂ NO ₅
322361	Me	H	ONa	S	C ₁₃ H ₁₀ Cl ₂ NNaO ₂ S
322363	H	Me	OH	S	C ₁₃ H ₁₁ Cl ₂ NO ₂ S
322364	Cl	H	OH	S	C ₁₂ H ₈ Cl ₃ NO ₂ S

SOURCE – Grünenthal.

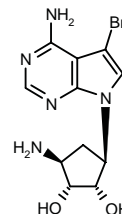
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1. Maul, C. et al. (Grünenthal GmbH) *Substd. derivs. of aminofuran-2-yl-acetic acid and aminothien-2-yl-acetic acid and the use thereof for treating migraines and pain.* DE 10059864, WO 0244171.

A-286501

321478

3(*S*)-Amino-5(*R*)-(4-amino-5-bromo-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)cyclopentane-1(*S*),2(*R*)-diol



C11 H14 Br N5 O2; Mol wt: 328.1686

ACTION – Orally active adenosine kinase inhibitor (IC₅₀ = 0.47 nM; K_i = 1.87 nM), with no significant activity up to 10 μM against adenosine receptors, adenosine transporter, adenosine deaminase and a range of other receptors, ion channels, proteins, neurotransmitter reuptake sites and enzymes. Compound exhibited dose-dependent antinociceptive activity in rats in models of acute thermal pain (ED₅₀ = 100 μmol/kg p.o.), inflammatory pain (carrageenan-induced hyperalgesia and carrageenan-induced paw edema; ED₅₀ = 1 and 20 μmol/kg p.o., respectively) and neuropathic pain (L5/L6 nerve ligation and streptozotocin-induced diabetic pain; ED₅₀ = 20 μmol/kg p.o. and 20 μmol/kg i.p., respectively). These effects of A-286501 were reversed by the nonselective adenosine receptor antagonist theophylline, but not blocked by the opioid antagonist naloxone. Compound had no significant effect on motor coordination at up to 300 μmol/kg p.o., although it significantly reduced spontaneous exploratory activity at 10 μmol/kg p.o.; no significant cardiovascular effects were seen. In addition, compound showed less potential to develop tolerance to its antinociceptive effects compared to morphine.

SOURCE – Abbott.

REFERENCES

1. Jarvis, M.F. et al. A novel adenosine kinase (AK) inhibitor, A-286501, is orally effective to reduce acute, inflammatory, and neuropathic pain in rats. Soc Neurosci Abst 2001, 27(1): 415.

2. Jarvis, M.F. et al. Analgesic and anti-inflammatory effects of A-286501, a novel orally active adenosine kinase inhibitor. Pain 2002, 96(1-2): 107.

AM-336

280433

ω-Conotoxin C VID
CVID

H-Cys-Lys-Ser-Lys-Gly-Ala-Lys-Cys-Ser-Lys-Leu-Met-Tyr-Asp-Cys-Cys-Ser-Gly-Ser-Cys-Ser-Gly-Thr-Val-Gly-Arg-Cys-NH₂ (1-16),(8-20),(15-27)-tris(disulfide)

C107 H179 N35 O36 S7; Mol wt: 2756.2620

ACTION – ω-Conotoxin isolated from the venom of the cone snail *Conus catus* with potent N-type calcium channel-blocking activity (IC₅₀ = 0.07 nM) and high selectivity over P/Q-type voltage-sensitive calcium channels (IC₅₀ = 55,000 nM). Compound inhibited electrically induced contractions of rat vas deferens (IC₅₀ = 18.4 nM) and K⁺-evoked release of substance P in rat spinal cord slices (EC₅₀ = 21.1 nM). In rats with adjuvant-induced inflammatory pain in the hindpaw, compound given intrathecally produced rapid and dose-dependent antinociceptive activity with an ED₅₀ of 0.110 nmol; a low incidence and severity of motor side effects was observed at doses of 0.18 nmol or below. In comparison with ziconotide, compound was approximately 100-fold more selective *in vitro* for N-type over P/Q-type calcium channels and exhibited better *in vivo* antinociceptive activity. Compound is presently in clinical trials for the treatment of severe morphine-resistant pain.

SOURCES – Amrad; University of Queensland, Queensland (AU).

REFERENCES

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2. Cabot, P. et al. Inhibition of K⁺-evoked substance P release from slices of rat spinal cord by the novel calcium channel blockers, AM336 and AM543 relative to ziconotide. 9th World Congr Pain (Aug 22-27, Vienna) 1999, 292.

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6. Wright, C.E. et al. Cardiovascular and autonomic effects of ω-conotoxins MVIIA and CVID in conscious rabbits and isolated tissue assays. Br J Pharmacol 2000, 131(7): 1325.

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8. Amrad product pipeline update. DailyDrugNews.com (Daily Essentials) 2001, Feb 21.

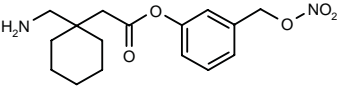
9. Amrad: Annual Report 1998. DailyDrugNews.com (Daily Essentials) 1999, Feb 25.

NCX-8001

322058

2-[1-(Aminomethyl)cyclohexyl]acetic acid 3-(nitrooxymethyl)phenyl ester

NCX-7001 (former code)



C16 H22 N2 O5; Mol wt: 322.3588

ACTION – Nitric oxide (NO)-releasing gabapentin derivative able to dose-dependently (10-100 mg/kg) improve pain-like responses to mechanical or cold stimulation in spinal cord-injured or sciatic nerve-injured rats when compared to the parent compound. Following repeated dosing in spinally injured rats, the antiallodynic effect of compound was sustained for 8 days whereas the effect of gabapentin only appeared following 3 days of treatment and lasted for 8 days. Potentially useful for the treatment of neuropathic pain.

SOURCE – NicOx.

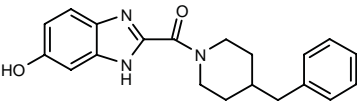
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RG-1103

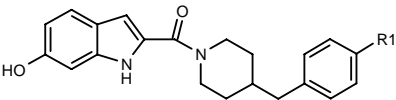
322002

1-(4-Benzylpiperidin-1-yl)-1-(6-hydroxy-1H-benzimidazol-2-yl)methanone



C20 H21 N3 O2; Mol wt: 335.4049

ACTION – NR2B subtype-selective NMDA receptor antagonist (IC₅₀ = 2.1 nM) with good oral bioavailability, analgesic activity and low side effect liability. Potentially useful for the treatment of neuropathic pain. Other related compounds are:



Compound	R1	Formula
RG-13579* [319535]	H	C ₂₁ H ₂₂ N ₂ O ₂
RG-13848 [322003]	F	C ₂₁ H ₂₁ FN ₂ O ₂

SOURCE – Gedeon Richter.

REFERENCES

1. Horvath, C. et al. (Gedeon Richter Ltd.) *Amine derivs. as NMDA receptor antagonists*. WO 0234718.

2. Farkas, S. et al. *NR2B-NMDA receptor antagonists for the treatment of chronic or neuropathic pain*. Pharmacologist 2002, 44(2, Suppl. 1): Abst 37.13.

*Identified compound **319535** Drug Data Rep 2002, 024(06): 0509.

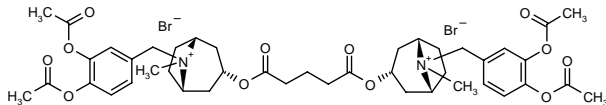
ADJUNCTS TO ANESTHESIA

ORG-25415

321503

trans,trans-Pentanedioic acid bis[8-(3,4-diacetoxybenzyl)-8-methyl-8-azoniabicyclo[3.2.1]octan-3-yl] diester dibromide

TAAC3



C43 H56 Br N2 O12; Mol wt: 952.7254

ACTION – Nondepolarizing neuromuscular blocker (NMB) able to produce rapid and ultrashort neuromuscular blockade with ED₉₀ values ranging from 90 µg/kg i.v. in guinea pigs to 470 µg/kg i.v. in pigs. It was slightly more potent than rocuronium in rats, guinea pigs and pigs, and less potent than rocuronium in rabbits, cats, dogs and monkeys. In addition, compound showed a faster onset (0.8-1.0 min) and shorter duration of action (1.8-3.5 min) compared to rocuronium, and a slight cumulative effect was seen following infusion, but not after repeated single doses. No autonomic nervous system side effects were observed except for a moderate cardiac vagal block, similar to that observed with rocuronium, at doses exceeding the ED₉₀ for neuromuscular blockade.

SOURCE – Organon.

REFERENCES

1. Gyermek, L. et al. (Newlaxant LLC) *Neuromuscular relaxants*. US 6376510.

2. Gyermek, L. et al. *Neuromuscular relaxants*. JP 2001521032, US 5990124, WO 9921854.

3. Gyermek, L. et al. *Neuromuscular pharmacology of TAAC3, a new nondepolarizing muscle relaxant with rapid onset and ultrashort duration of action*. Anesth Analg 2002, 94(4): 879.

4. Gyermek, L. et al. *TAAC3: An ultrashort-acting nondepolarizing muscle relaxant in animals*. Anesth Analg 2001, 92(Suppl.): Abst S200.

5. Park, H.S. et al. *3H-Epipatidine in torpedo tissue by new rapidly acting muscle relaxants*. FASEB J 2001, 15(4): Abst 456.13.

6. Van Egmond, J. et al. *New fast neuromuscular blocking agent TAAC3 in the anaesthetized monkey*. 7th Int Neuromuscular Meet (June 21-24, Belfast) 2001, Abst 2.

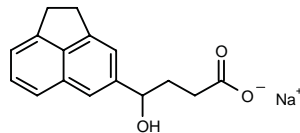
7. Van Egmond, J. et al. *New fast neuromuscular blocking agent, TAAC3, in the anaesthetized dog*. 7th Int Neuromuscular Meet (June 21-24, Belfast) 2001, Abst 3.

PSYCHOPHARMACOLOGIC DRUGS

TREATMENT OF SLEEP DISORDERS

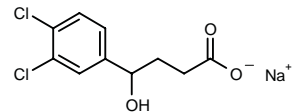
322128

4-(1,2-Dihydroacenaphthylen-4-yl)-4-hydroxybutyric acid sodium salt



C16 H15 Na O3; Mol wt: 278.2815

ACTION – Agent with affinity for γ-hydroxybutyrate (GHB) receptors (IC₅₀ = 0.08 µM), found to induce an increase in the duration of sleep when administered to rats at 0.15 mmol/kg i.p. Potentially useful for the treatment of CNS disorders including sleep disorders, anxiety, epilepsy, depression, ischemic stroke, eating disorders and drug abuse, and also as modulators of growth hormone secretion, neuroleptic activity and circadian rhythm. Another exemplified compound is:



322130: C10 H9 Cl2 Na O3

SOURCE – Université Louis Pasteur, Strasbourg (FR).

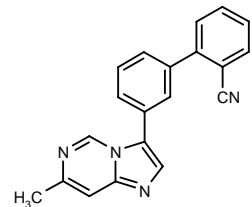
REFERENCES

1. Bourguignon, J.-J. et al. (Université Louis Pasteur) *Derivs. of 4-hydroxybutanoic acid and of its higher homologue as ligands of γ-hydroxybutyrate (GHB) receptors, pharmaceutical compsns. containing same and pharmaceutical uses*. WO 0242250.

ANXIOLYTICS

321073

3'-(7-Methylimidazo[1,2-c]pyrimidin-3-yl)biphenyl-2-carbonitrile



C20 H14 N4; Mol wt: 310.3586

REFERENCES

1. Horvath, C. et al. (Gedeon Richter Ltd.) *Amine derivs. as NMDA receptor antagonists*. WO 0234718.

2. Farkas, S. et al. *NR2B-NMDA receptor antagonists for the treatment of chronic or neuropathic pain*. Pharmacologist 2002, 44(2, Suppl. 1): Abst 37.13.

*Identified compound **319535** Drug Data Rep 2002, 024(06): 0509.

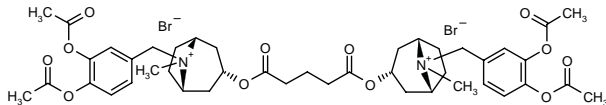
ADJUNCTS TO ANESTHESIA

ORG-25415

321503

trans,trans-Pentanedioic acid bis[8-(3,4-diacetoxybenzyl)-8-methyl-8-azoniabicyclo[3.2.1]octan-3-yl] diester dibromide

TAAC3



C43 H56 Br N2 O12; Mol wt: 952.7254

ACTION – Nondepolarizing neuromuscular blocker (NMB) able to produce rapid and ultrashort neuromuscular blockade with ED₉₀ values ranging from 90 µg/kg i.v. in guinea pigs to 470 µg/kg i.v. in pigs. It was slightly more potent than rocuronium in rats, guinea pigs and pigs, and less potent than rocuronium in rabbits, cats, dogs and monkeys. In addition, compound showed a faster onset (0.8-1.0 min) and shorter duration of action (1.8-3.5 min) compared to rocuronium, and a slight cumulative effect was seen following infusion, but not after repeated single doses. No autonomic nervous system side effects were observed except for a moderate cardiac vagal block, similar to that observed with rocuronium, at doses exceeding the ED₉₀ for neuromuscular blockade.

SOURCE – Organon.

REFERENCES

1. Gyermek, L. et al. (Newlaxant LLC) *Neuromuscular relaxants*. US 6376510.

2. Gyermek, L. et al. *Neuromuscular relaxants*. JP 2001521032, US 5990124, WO 9921854.

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5. Park, H.S. et al. *3H-EpiBatidine in torpedo tissue by new rapidly acting muscle relaxants*. FASEB J 2001, 15(4): Abst 456.13.

6. Van Egmond, J. et al. *New fast neuromuscular blocking agent TAAC3 in the anaesthetized monkey*. 7th Int Neuromuscular Meet (June 21-24, Belfast) 2001, Abst 2.

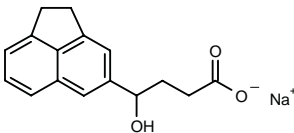
7. Van Egmond, J. et al. *New fast neuromuscular blocking agent, TAAC3, in the anaesthetized dog*. 7th Int Neuromuscular Meet (June 21-24, Belfast) 2001, Abst 3.

PSYCHOPHARMACOLOGIC DRUGS

TREATMENT OF SLEEP DISORDERS

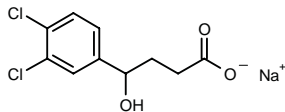
322128

4-(1,2-Dihydroacenaphthylen-4-yl)-4-hydroxybutyric acid sodium salt



C16 H15 Na O3; Mol wt: 278.2815

ACTION – Agent with affinity for γ-hydroxybutyrate (GHB) receptors (IC₅₀ = 0.08 µM), found to induce an increase in the duration of sleep when administered to rats at 0.15 mmol/kg i.p. Potentially useful for the treatment of CNS disorders including sleep disorders, anxiety, epilepsy, depression, ischemic stroke, eating disorders and drug abuse, and also as modulators of growth hormone secretion, neuroleptic activity and circadian rhythm. Another exemplified compound is:



322130: C10 H9 Cl2 Na O3

SOURCE – Université Louis Pasteur, Strasbourg (FR).

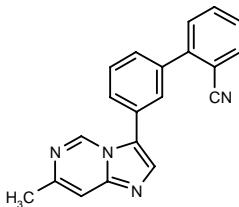
REFERENCES

1. Bourguignon, J.-J. et al. (Université Louis Pasteur) *Derivs. of 4-hydroxybutanoic acid and of its higher homologue as ligands of γ-hydroxybutyrate (GHB) receptors, pharmaceutical compsns. containing same and pharmaceutical uses*. WO 0242250.

ANXIOLYTICS

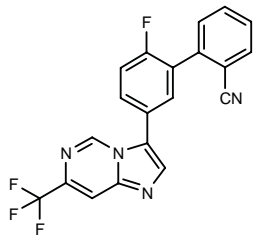
321073

3'-(7-Methylimidazo[1,2-c]pyrimidin-3-yl)biphenyl-2-carbonitrile



C20 H14 N4; Mol wt: 310.3586

ACTION – Agent with affinity for the α 2 and/or α 3 subunits of GABA_A receptors, potentially useful for the treatment of anxiety and convulsions. Another exemplified imidazo-pyrimidine derivative is:



321074: C20 H10 F4 N4

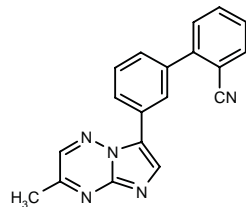
SOURCE – Merck Sharp & Dohme.

REFERENCES

1. Hallett, D.J. et al. (Merck Sharp & Dohme Ltd.) *Imidazo-pyrimidine derivs. as ligands for GABA receptors*. WO 0238569.

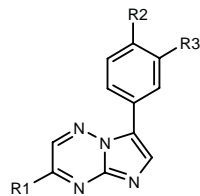
321075

3'-(3-Methylimidazo[1,2-*b*][1,2,4]triazin-7-yl)biphenyl-2-carbonitrile



C19 H13 N5; Mol wt: 311.3467

ACTION – Agent with affinity for the α 2 and/or α 3 subunits of GABA_A receptors, potentially useful for the treatment of anxiety and convulsions. Other exemplified imidazo-triazine derivatives are:



Compound	R1	R2	R3	Formula
321076	CF2Me	F	3-Pyr	C ₁₈ H ₁₂ F ₃ N ₅
321077	CH(Me)2OH	F	3-CN-2-Pyr	C ₂₀ H ₁₅ FN ₆ O
321078	CH(Me)2OH	F	2-Pyr	C ₁₉ H ₁₆ FN ₅ O
321080	CF3	H	2-Me-2H-1,2,3-triazol-4-yl	C ₁₅ H ₁₀ F ₃ N ₇
321081	CF3	F	1,2,4-triazol-1-yl	C ₁₄ H ₇ F ₄ N ₇
321082	CF3	F	5-[N(Me)2CO]-2-thiazolyl	C ₁₈ H ₁₂ F ₄ N ₆ OS
321083	CF3	H	4-CHO-Ph	C ₁₉ H ₁₁ F ₃ N ₄ O
321084	CF3	F	4-OH-Ph	C ₁₈ H ₁₀ F ₄ N ₄ O

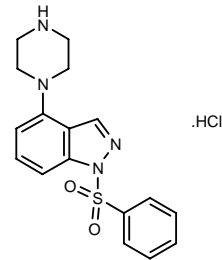
SOURCE – Merck Sharp & Dohme.

REFERENCES

1. Bettati, M. et al. (Merck Sharp & Dohme Ltd.) *Imidazo-triazine derivs. as ligands for GABA receptors*. WO 0238568.

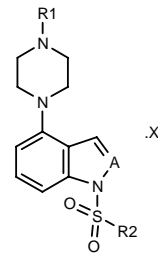
321348

1-(Phenylsulfonyl)-4-(1-piperazinyl)-1*H*-indazole hydrochloride



C17 H18 N4 O2 S . HCl; Mol wt: 378.8821

ACTION – Agent with affinity for 5-HT₆ receptors (K_i = 0.3 nM), potentially useful for the treatment of motor disorders, anxiety, schizophrenia, depression, Alzheimer's disease and Parkinson's disease. Other exemplified compounds are:



Compound	R1	R2	A	X	Formula
321349	H	6-Cl-imidazo[2,1-b]-thiazol-5-yl	CH		C ₁₇ H ₁₆ ClN ₅ O ₂ S ₂
321350	H	4-NH2-Ph	CH		C ₁₈ H ₂₀ N ₄ O ₂ S
321352	3-Pyr-CH2	2-Br-Ph	CH		C ₂₄ H ₂₃ BrN ₄ O ₂ S
321353	CH2CH2Ph	Ph	N	HCl	C ₂₅ H ₂₆ N ₄ O ₂ S.HCl

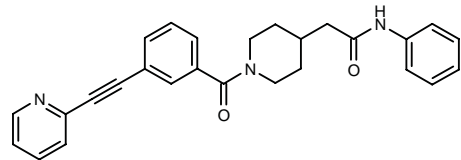
SOURCE – Wyeth.

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1. Kelly, M.G. and Cole, D.C. (American Home Products Corp.) *1-Aryl- or 1-alkylsulfonyl-heterocycly/benzazoles as 5-hydroxytryptamine-6 ligands*. WO 0236562.

322031

N-Phenyl-2-[1-[3-(pyridin-2-ylethynyl)benzoyl]piperidin-4-yl]acetamide



C27 H25 N3 O2; Mol wt: 423.5135

ACTION – Agent for the treatment of anxiety and depression, as well as other neurological disorders such as dementia, bipolar disorder, schizophrenia, emesis, migraine, itching, acute pain, neuropathic pain and movement disorders. Compound demonstrated *in vivo* activity in the mouse DOI-induced head shake model at 40 mg/kg p.o. and 100 mg/kg i.p., the senktide-induced head shake model at 10 mg/kg p.o. and the elevated plus-maze test at 10 mg/kg p.o. It also inhibited cisplatin-induced retching behavior at 20 mg/kg s.c., indicating antiemetic activity.

SOURCE – Ortho-McNeil.

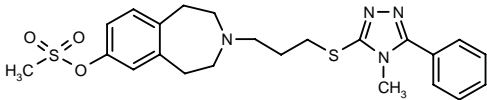
REFERENCES

1. Kordik, C.P. et al. (Ortho-McNeil Pharmaceutical, Inc.) *Novel amidoalkyl-piperidine and amidoalkyl-piperazine derivs. useful for the treatment of nervous system disorders.* WO 0240466.

ANTIPSYCHOTIC DRUGS

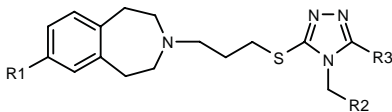
321794

Methanesulfonic acid 3-[3-(4-methyl-5-phenyl-4*H*-1,2,4-triazol-3-ylsulfanyl)propyl]-2,3,4,5-tetrahydro-1*H*-3-benzazepine-7-yl ester



C23 H28 N4 O3 S2; Mol wt: 472.6312

ACTION – Antipsychotic agent that acts as a dopamine D3 receptor antagonist, potentially useful for the treatment of schizophrenia and drug abuse. Other exemplified tetrahydrobenzazepine derivatives are:



Compound	R1	R2	R3	Formula
321795	OSO2Me	H	4-F-Ph	C ₂₃ H ₂₇ FN ₄ O ₃ S ₂
321796	5-Me-2-oxazolyl	H	6-quinolyl	C ₂₉ H ₃₀ N ₆ OS
321797	SO2Me	H	1-Me-5-indolyl	C ₂₆ H ₃₁ N ₅ O ₂ S ₂
321798	SO2Et	H	4-benzofuryl	C ₂₆ H ₃₀ N ₄ O ₃ S ₂
321799	SO2Et	H	7-benzofuryl	C ₂₆ H ₃₀ N ₄ O ₃ S ₂
321801	5-Me-3-isoxazolyl	H	2-Me-6-quinolyl	C ₃₀ H ₃₂ N ₆ OS
321802	5-Me-3-isoxazolyl	H	4-CN-Ph	C ₂₇ H ₂₈ N ₆ OS
321803	5-Me-2-oxazolyl	vinyl	6-quinolyl	C ₃₁ H ₃₂ N ₆ OS

SOURCE – GlaxoSmithKline.

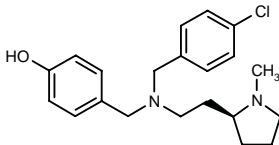
REFERENCES

1. Hadley, M.S. et al. (GlaxoSmithKline plc) *Tetrahydrobenzazepine derivs. useful as modulators of dopamine D₃ receptors (antipsychotic agents).* WO 0240471.

TREATMENT OF MOOD DISORDERS

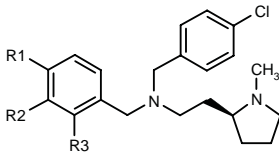
321385

4-[*N*-(4-Chlorobenzyl)-*N*-[2-[1-methylpyrrolidin-2(*S*)-yl]-ethyl]aminomethyl]phenol



C21 H27 Cl N2 O; Mol wt: 358.9103

ACTION – Potent 5-HT₇ receptor antagonist (K_i = 1.9 nM) with selectivity over 5-HT_{1A} (> 2,000 fold), 5-HT_{2A} (78-fold), 5-HT₆ (93-fold) and dopamine D2 receptors (690-fold). Potentially useful for the treatment of pain, schizophrenia, depression and sleep disorders. Other exemplified 2-(aminoalkyl)pyrrolidine derivatives are:



Compound	R1	R2	R3	Formula
321386	H	OH	H	C ₂₁ H ₂₇ ClN ₂ O
321387	OH	H	Cl	C ₂₁ H ₂₆ Cl ₂ N ₂ O
321388	OH	Cl	H	C ₂₁ H ₂₆ Cl ₂ N ₂ O
321389	OH	OMe	H	C ₂₂ H ₂₉ ClN ₂ O ₂

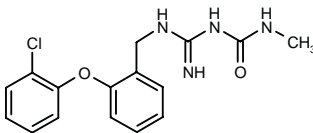
SOURCE – Pfizer.

REFERENCES

1. Rui, Y. et al. (Pfizer Inc.) *Aminoalkylpyrrolidine serotonin receptor ligands and compsns., their pharmaceutical uses, and methods for their synthesis.* WO 0236560.

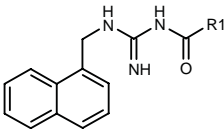
321390

1-[1-[2-(2-Chlorophenoxy)benzylamino]-1-iminomethyl]-3-methylurea

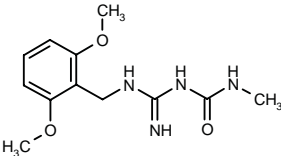


C16 H17 Cl N4 O2; Mol wt: 332.7893

ACTION – Potent 5-HT₇ receptor antagonist (K_i = 6.3 nM) with selectivity over 5-HT_{1A} (146-fold), 5-HT_{2A} (46-fold), 5-HT₆ (92-fold) and dopamine D2 receptors (> 390-fold). Potentially useful for the treatment of pain, schizophrenia, depression and sleep disorders. Other exemplified amidino urea derivatives are:



Compound	R1	Formula
321391	4-PhCH2-1-Piz	C ₂₄ H ₂₇ N ₅ O
321392	4-(PhCH=CHCH2)-1-Piz	C ₂₆ H ₂₉ N ₅ O
321393	4-(PhCH2)-1-Pip	C ₂₅ H ₂₈ N ₄ O



321394: C12 H18 N4 O3

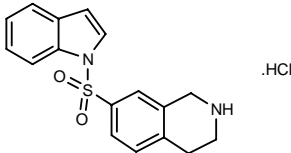
SOURCE – Pfizer.

REFERENCES

1. Hong, Y. et al. (Pfizer Inc.) *Amidino-urea serotonin receptor ligands and compsns., their pharmaceutical uses, and methods for their synthesis.* WO 0236554.

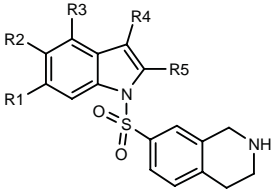
321686

7-(1*H*-Indol-1-ylsulfonyl)-1,2,3,4-tetrahydroisoquinoline hydrochloride



C17 H16 N2 O2 S . HCl; Mol wt: 348.8523

ACTION – Agent with affinity for 5-HT₆ receptors (pK_i = 8.2-8.9), potentially useful for the treatment of CNS disorders including depression, anxiety, Alzheimer’s disease, age-related cognitive decline, attention deficit hyperactivity disorder, mild cognitive impairment and schizophrenia. Other exemplified isoquinoline derivatives are:



Compound	R1	R2	R3	R4	R5	Formula
321687	H	H	H	-(CH2)4-		C ₂₁ H ₂₂ N ₂ O ₂ S
321688	H	H	H	Me	H	C ₁₈ H ₁₈ N ₂ O ₂ S
321689	H	H	H	Ph	H	C ₂₃ H ₂₀ N ₂ O ₂ S
321690	H	F	H	H	Ph	C ₂₃ H ₁₉ FN ₂ O ₂ S
321691	Cl	H	H	H	H	C ₁₇ H ₁₅ ClN ₂ O ₂ S
321692	H	H	Cl	H	H	C ₁₇ H ₁₅ ClN ₂ O ₂ S
321693	OMe	H	H	H	H	C ₁₈ H ₁₈ N ₂ O ₃ S
321694	Me	H	H	H	H	C ₁₈ H ₁₈ N ₂ O ₂ S
321695	H	H	Me	H	H	C ₁₈ H ₁₈ N ₂ O ₂ S
321696	F	H	H	H	H	C ₁₇ H ₁₅ FN ₂ O ₂ S
321697	F	F	H	H	H	C ₁₇ H ₁₄ F ₂ N ₂ O ₂ S
321698	CF3	H	H	H	H	C ₁₈ H ₁₅ F ₃ N ₂ O ₂ S

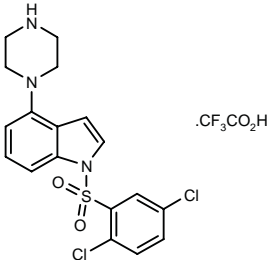
SOURCE – GlaxoSmithKline.

REFERENCES

1. Bromidge, S.M. and Moss, S.F. (GlaxoSmithKline plc) *Isoquinoline derivs. useful in the treatment of CNS disorders.* WO 0242293.

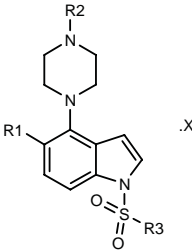
321699

1-(2,5-Dichlorophenylsulfonyl)-4-(1-piperazinyl)-1*H*-indole trifluoroacetate



C18 H17 Cl2 N3 O2 S . C2 H F3 O2; Mol wt: 524.3452

ACTION – Agent with affinity for 5-HT₆ receptors (pK_i = 8.8-9.7), potentially useful for the treatment of CNS disorders including depression, anxiety, Alzheimer’s disease, age-related cognitive decline, attention deficit hyperactivity disorder, mild cognitive impairment and schizophrenia. Other exemplified compounds are:



Compound	R1	R2	R3	X	Formula
321700	H	H	3-Br-5-Cl-2-thienyl	CF3CO2H	C ₁₆ H ₁₅ BrClN ₃ O ₂ S ₂ .C ₂ HF ₃ O ₂
321701	H	H	2,1,3-benzoxadiazol-4-yl	CF3CO2H	C ₁₈ H ₁₇ N ₅ O ₃ S .C ₂ HF ₃ O ₂
321703	H	Me	2-thienyl		C ₁₇ H ₁₉ N ₃ O ₂ S ₂
321704	H	Me	2-CF3-Ph		C ₁₉ H ₁₈ F ₃ N ₃ O ₂ S
321705	Cl	H	2-Pyr	HCl	C ₁₇ H ₁₇ ClN ₄ O ₂ S .HCl

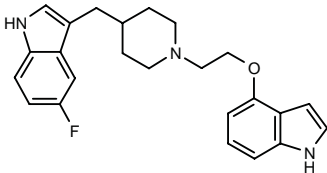
SOURCE – GlaxoSmithKline.

REFERENCES

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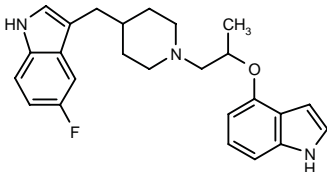
322032

5-Fluoro-3-[1-[2-(1*H*-indol-4-yloxy)ethyl]piperidin-4-ylmethyl]-1*H*-indole



C24 H26 F N3 O; Mol wt: 391.4874

ACTION – Agent with dual activity at 5-HT_{1A} receptors and the 5-HT transporter, potentially useful for the treatment of depression and anxiety, as well as other 5-HT-mediated neurological disorders. It gave K_i values of 0.08 and 47 nM, respectively, at the 5-HT transporter and the 5-HT_{1A} receptor in binding assays. Another specifically claimed piperidinyl indole is:



322033: C₂₅ H₂₈ F N₃ O

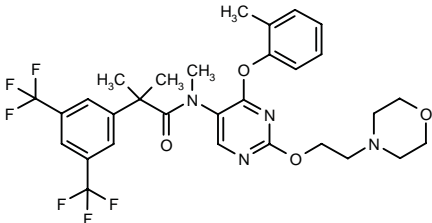
SOURCE – Wyeth.

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1. Mewshaw, R.E. et al. (Wyeth) Aryloxy piperidinyl indoles for treating depression. WO 0240465.

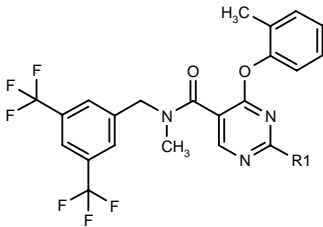
322039

2-[3,5-Bis(trifluoromethyl)phenyl]-N,2-dimethyl-N-[4-(2-methylphenoxy)-2-[2-(4-morpholinyl)ethoxy]pyrimidin-5-yl]propionamide

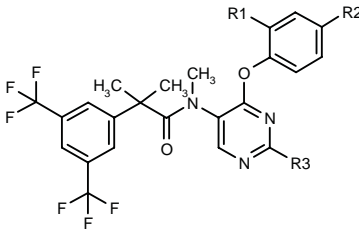


C₃₀ H₃₂ F₆ N₄ O₄; Mol wt: 626.5948

ACTION – Tachykinin NK₁ receptor antagonist that gave a pK_i of 9.10 at human NK₁ receptors expressed in CHO cells. Particularly useful for the treatment of CNS disorders such as depression and emesis. Other exemplified pyrimidine derivatives include the following:



Compound	R1	Formula
322040	4-Me-1-Piz	C ₂₇ H ₂₇ F ₆ N ₅ O ₂
322041	4-morpholinyl-CH ₂ CH ₂ O	C ₂₈ H ₂₈ F ₆ N ₄ O ₄



Compound	R1	R2	R3	Formula
322042	Me	H	4-Me-1-Piz	C ₂₉ H ₃₁ F ₆ N ₅ O ₂
322043	H	F	O(CH ₂) ₃ N(Me) ₂	C ₂₈ H ₂₈ F ₇ N ₄ O ₃

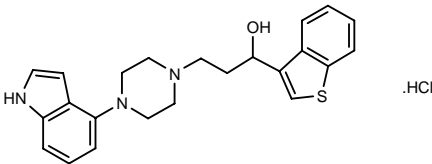
SOURCE – Roche.

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1. Stadler, H. (F. Hoffmann-La Roche AG) Pyrimidine derivs. WO 0242280.

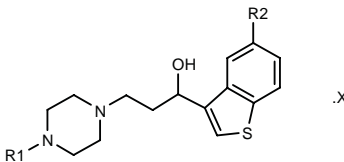
322345

1-(1-Benzothien-3-yl)-3-[4-(1H-indol-4-yl)piperazin-1-yl]propan-1-ol hydrochloride



C₂₃ H₂₅ N₃ O S . HCl; Mol wt: 427.9974

ACTION – Agent with dual activity as a 5-HT reuptake inhibitor and modulator of 5-HT_{1A} receptors. In binding assays, the compound gave K_i values of 4.1 and 5.5 nM, respectively, for the 5-HT transporter and 5-HT_{1A} receptors in rat cortical membranes. Potentially useful for the treatment of depression, psychosis, anxiety, panic attacks, obsessive-compulsive disorders and eating disorders. Other exemplified benzothiophene derivatives are:



Compound	R1	R2	X	Formula
322346	8-quinolyl	F		C ₂₄ H ₂₄ FN ₃ OS
322347	4-indolyl	F		C ₂₃ H ₂₄ FN ₃ OS
322348	2-Me-8-quinolyl	F		C ₂₅ H ₂₆ FN ₃ OS
322349	8-quinolyl	H	HCl	C ₂₄ H ₂₆ N ₃ OS.HCl

SOURCE – Vita-Invest.

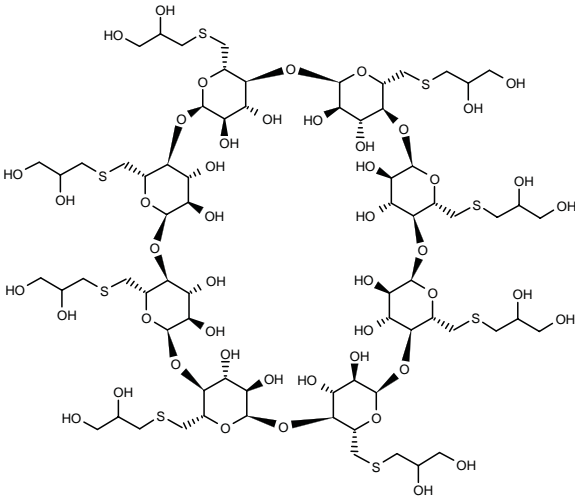
REFERENCES

1. Del Castillo Nieto, J.C. et al. (Vita-Invest, SA) Benzothiophene deriv. cpds., process of preparation and use thereof. WO 0244170.

ORG-26276

321429

6*A,6B,6C,6D,6E,6F,6G,6H*-Octakis-*S*-(2,3-dihydroxypropyl)-6*A,6B,6C,6D,6E,6F,6G*-octasulfanyl- γ -cyclodextrin



C72 H128 O48 S8; Mol wt: 2018.2830

ACTION – γ -Cyclodextrin derivative with cortisol-sequestering activity, potentially useful for the treatment of depression, Cushing's syndrome, schizophrenia and anxiety. It gave a cortisol binding constant (K_a) > 100,000 M⁻¹, thus proving its sequestering potential. Administration of compound to rats and pigs (20 mg/kg by i.v. bolus) resulted in 10- and 3-fold increases, respectively, in the urinary excretion of cortisol.

SOURCE – Akzo Nobel.

REFERENCES

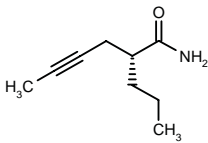
1. Zhang, M. et al. (Akzo Nobel N.V.) *Use of cortisol-sequestering agents for the treatment of hypercortisolaemia related disorders*. WO 0236105.

NEUROLOGIC DRUGS

ANTIEPILEPTIC DRUGS

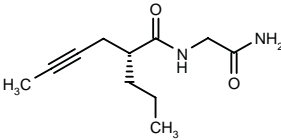
321329

2(*R*)-Propyl-4-hexynamide



C9 H15 N O; Mol wt: 153.2235

ACTION – Anticonvulsant proven to provide complete protection against pentylenetetrazol-induced seizures in mice at a dose of 1400 μ mol/kg i.p. and 90% protection against maximal electroshock-induced seizures following a dose of 1800 μ mol/kg orally. Potentially useful for the treatment of seizures, epilepsy, migraine, neuropathic pain, restlessness syndrome and psychiatric disorders, as well as for providing neuroprotection against ischemic insults. Another exemplified alkynyl amide is:



321331: C11 H18 N2 O2

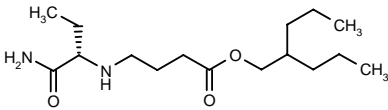
SOURCE – Abbott.

REFERENCES

1. Bennani, Y.L. (Abbott Laboratories) *Alkynyl amides and their therapeutic applications*. WO 0236546.

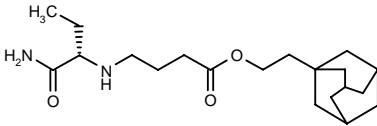
322038

4-[1(*S*)-Carbamoylpropylamino]butyric acid 2-propylpentyl ester



C16 H32 N2 O3; Mol wt: 300.4398

ACTION – Putative GABA_A receptor antagonist, potentially useful for the treatment of epilepsy, migraine, bipolar disorders and chronic and neuropathic pain. In the audiogenic seizure test in mice, the compound displayed an ED₅₀ value of 120 μ mol/kg i.p. Another exemplified *N*-alkylated GABA compound is:



322270: C20 H34 N2 O3

SOURCE – UCB.

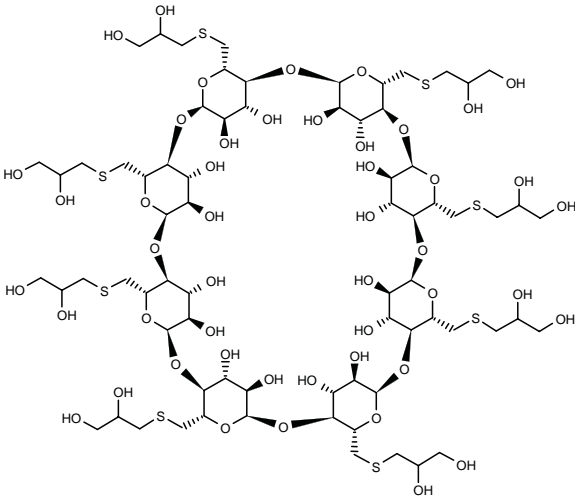
REFERENCES

1. Kenda, B. et al. (UCB SA) *N-Alkylated GABA cpds., processes for their preparation and their use as medicaments*. WO 0242256.

ORG-26276

321429

6*A,6B,6C,6D,6E,6F,6G,6H*-Octakis-*S*-(2,3-dihydroxypropyl)-6*A,6B,6C,6D,6E,6F,6G*-octasulfanyl- γ -cyclodextrin



C72 H128 O48 S8; Mol wt: 2018.2830

ACTION – γ -Cyclodextrin derivative with cortisol-sequestering activity, potentially useful for the treatment of depression, Cushing's syndrome, schizophrenia and anxiety. It gave a cortisol binding constant (K_a) > 100,000 M⁻¹, thus proving its sequestering potential. Administration of compound to rats and pigs (20 mg/kg by i.v. bolus) resulted in 10- and 3-fold increases, respectively, in the urinary excretion of cortisol.

SOURCE – Akzo Nobel.

REFERENCES

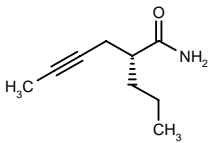
1. Zhang, M. et al. (Akzo Nobel N.V.) *Use of cortisol-sequestering agents for the treatment of hypercortisolaemia related disorders*. WO 0236105.

NEUROLOGIC DRUGS

ANTIEPILEPTIC DRUGS

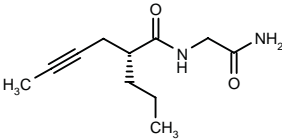
321329

2(*R*)-Propyl-4-hexynamide



C9 H15 N O; Mol wt: 153.2235

ACTION – Anticonvulsant proven to provide complete protection against pentylenetetrazol-induced seizures in mice at a dose of 1400 μ mol/kg i.p. and 90% protection against maximal electroshock-induced seizures following a dose of 1800 μ mol/kg orally. Potentially useful for the treatment of seizures, epilepsy, migraine, neuropathic pain, restlessness syndrome and psychiatric disorders, as well as for providing neuroprotection against ischemic insults. Another exemplified alkynyl amide is:



321331: C11 H18 N2 O2

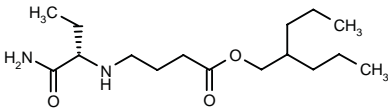
SOURCE – Abbott.

REFERENCES

1. Bennani, Y.L. (Abbott Laboratories) *Alkynyl amides and their therapeutic applications*. WO 0236546.

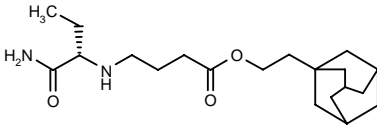
322038

4-[1(*S*)-Carbamoylpropylamino]butyric acid 2-propylpentyl ester



C16 H32 N2 O3; Mol wt: 300.4398

ACTION – Putative GABA_A receptor antagonist, potentially useful for the treatment of epilepsy, migraine, bipolar disorders and chronic and neuropathic pain. In the audiogenic seizure test in mice, the compound displayed an ED₅₀ value of 120 μ mol/kg i.p. Another exemplified *N*-alkylated GABA compound is:



322270: C20 H34 N2 O3

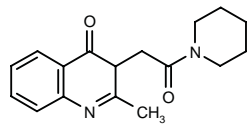
SOURCE – UCB.

REFERENCES

1. Kenda, B. et al. (UCB SA) *N-Alkylated GABA cpds., processes for their preparation and their use as medicaments*. WO 0242256.

322452

2-Methyl-3-[2-oxo-2-(1-piperidinyl)ethyl]quinolin-4(3H)-one



C17 H20 N2 O2; Mol wt: 284.3570

ACTION – Antiepileptic agent, an AMPA receptor antagonist able to selectively inhibit the fast desensitizing component of AMPA-induced calcium influx on AMPA receptors. *In vivo* compound exhibited antiepileptic activity in a low-magnesium model of epilepsy.

SOURCE – Hungarian Academy of Sciences, Budapest (HU).

REFERENCES

1. Lasztocki, B. et al. *A new ionotropic glutamate receptor subtype antagonist inhibits hippocampal seizures in vitro*. 3rd Forum Eur Neurosci (July 13-17, Paris) 2002, Abst 223.3.

2. Lasztocki, B. et al. *A glutamate receptor subtype antagonist inhibits seizures in rat hippocampal slices*. NeuroReport 2002, 13(3): 351.

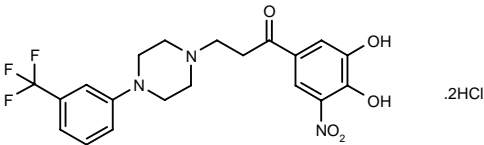
3. Szárics, E. et al. *Quinazalone-alkyl-carboxylic acid derivatives inhibit transmembrane Ca²⁺ ion flux to (+)-(S)-α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid*. Mol Pharmacol 2001, 59(4): 920.

TREATMENT OF EXTRAPYRAMIDAL MOVEMENT DISORDERS

BIA-3-335

315058

1-(3,4-Dihydroxy-5-nitrophenyl)-3-[4-[3-(trifluoromethyl)phenyl]piperazin-1-yl]propan-1-one dihydrochloride



C20 H20 F3 N3 O5 . 2HCl; Mol wt: 512.3098

ACTION – Potent, reversible and fast/tight-binding inhibitor of catechol *O*-methyltransferase (COMT; K_i = 6.0 nM) showing competitive inhibition of the substrate binding site and uncompetitive inhibition of the cosubstrate *S*-adenosyl-L-methionine (SAM) binding site. Potentially useful for the treatment of Parkinson's disease.

SOURCES – Bial; Portela.

REFERENCES

1. Learmonth, D.A. and Soares Da Silva, P.M.V.A. (Portela & Ca., SA) *Novel subst. nitrocatechols, their use in the treatment of some central and peripheral nervous system disorders and pharmaceutical compsns. containing them*. EP 1167342, WO 0198251.

2. Bonifácio, M.J. et al. *Characterization of the inhibition mechanism of catechol-O-methyltransferase with two novel inhibitors, BIA 3-202 and BIA 3-335*. Br J Pharmacol 2002, 135(Suppl.): Abst 211P.

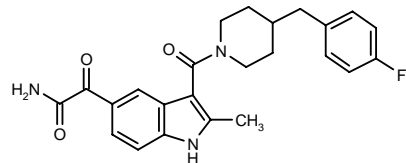
3. Rodrigues, M.L. et al. *Crystallization and preliminary crystallographic characterization of catechol-O-methyltransferase in complex with its cosubstrate and an inhibitor*. Acta Crystallograph Sect D 2001, 57(Part 6): 906.

4. Soares-da-Silva, P. et al. *Kinetics and crystal structure of catechol-O-methyltransferase complex with co-substrate and a novel inhibitor with potential therapeutic application*. Pharmacologist 2002, 44(2, Suppl. 1): Abst 32.6.

TREATMENT OF IMMUNOLOGIC NEUROMUSCULAR DISORDERS

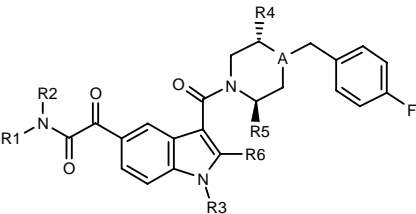
322079

2-[3-[4-(4-Fluorobenzyl)piperidin-1-ylcarbonyl]-2-methyl-1*H*-indol-5-yl]-2-oxoacetamide



C24 H24 F N3 O3; Mol wt: 421.4696

ACTION – A compound with p38α kinase-inhibitory activity, potentially useful for the treatment of inflammatory and proliferative disorders such as multiple sclerosis, inflammatory bowel disease, rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gout, sepsis, septic shock, asthma, adult respiratory distress syndrome, stroke, reperfusion injury, CNS injury, psoriasis, restenosis, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcosis, bone resorption, transplant rejection, Crohn's disease, ulcerative colitis, Alzheimer's disease and fever. Other exemplified compounds are:



Compound	R1	R2	R3	R4	R5	R6	A	Formula
322080	Me	Et	H	H	H	Me	CH	C ₂₇ H ₃₀ FN ₃ O ₃
322081	H	H	H	H	H	H	CH	C ₂₃ H ₂₂ FN ₃ O ₃
322083	Me	Et	H	H	H	H	CH	C ₂₆ H ₂₈ FN ₃ O ₃
322084	Me	Me	Me	H	H	Me	CH	C ₂₇ H ₃₀ FN ₃ O ₃
322085	H	H	H	Me	Me	Me	N	C ₂₆ H ₂₇ FN ₃ O ₃
322086	Me	Et	H	Me	Me	Me	N	C ₂₈ H ₃₃ FN ₃ O ₃
322087	Me	Me	Me	Me	Me	Me	N	C ₂₈ H ₃₃ FN ₃ O ₃
322088	Me	Me	SO ₂ N(Me) ₂	Me	Me	H	N	C ₂₈ H ₃₄ FN ₅ O ₃ S

SOURCE – Scios.

REFERENCES

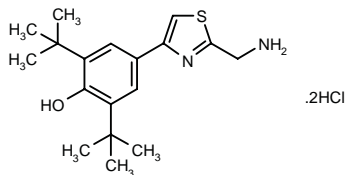
1. Dugar, S. et al. (Scios Inc.) *Inhibitors of p38 kinase*. WO 0242292.

TREATMENT OF
NEURODEGENERATIVE DISEASES

BN-82451

322450

4-[2-(Aminomethyl)thiazol-4-yl]-2,6-di-*tert*-butylphenol dihydrochloride



C18 H26 N2 O S . 2HCl; Mol wt: 391.4042

ACTION – Neuroprotective agent with antioxidant, cyclooxygenase-inhibitory and selective Na⁺ channel-blocking activities. *In vitro*, compound (20-25 μM) prevented rat liver mitochondrial swelling induced by *tert*-butyl hydroperoxide (*t*-BH) and *t*-BH-induced cell death in human SH-SY5Y neuroblastoma cells. *In vivo*, compound protected mice from MPTP-induced dopamine loss and KCN-induced death (ED₅₀ = 7.4 and 4.1 mg/kg p.o., respectively). In the KCN model, the compound showed significant efficacy when given up to 6 h before the mitochondrial toxin. BN-82451 was also effective against maximal electroshock seizures (ED₅₀ = 20.9 mg/kg) and NMDA-induced lethality (ED₅₀ > 30 mg/kg) in mice. Behavioral side effects such as ataxia were seen only at high doses (ED₅₀ = 224 mg/kg in the rotarod test) and a large therapeutic index (TI > 30) was calculated for compound. Potentially useful for the treatment of neurodegenerative diseases such as amyotrophic lateral sclerosis.

SOURCE – Beaufour-Ipsen.

REFERENCES

1. Chabrier de Lassauniere, P.-E. et al. (SCRAS [Société de Conseils de Recherches et d'Applications Scientifiques]) *5-Membered heterocycle derivs., production thereof and use thereof as medicaments*. WO 0126656.

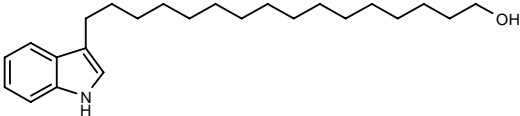
2. Delaflotte, S. et al. *Effects of a new neuroprotective agent, BN82451, on tertibutyl hydroperoxide-induced swelling of isolated mitochondria and cytotoxicity in human SH-SY5Y neuroblastoma cells*. 3rd Forum Eur Neurosci (July 13-17, Paris) 2002, Abst 149.9.

3. Spinnewyn, B. et al. *BN82451: A new neuroprotective agent with a large therapeutic index*. 3rd Forum Eur Neurosci (July 13-17, Paris) 2002, Abst 149.27.

TREATMENT OF
COGNITION DISORDERS

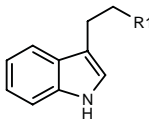
321164

16-(1*H*-Indol-3-yl)hexadecan-1-ol



C24 H39 N O; Mol wt: 357.5781

ACTION – A compound with neurotrophic, antioxidant and antitumor activity, shown to promote neurite outgrowth in primary cultured fetal rat nerve cells. It also demonstrated a protective effect against free radical-induced hemolysis in human blood cells, and induced differentiation and apoptosis in human neuroblastoma Lan-1 cells. Potentially useful for the treatment of encephalopathies such as dementia, and also brain tumors. Other exemplified compounds are:



Compound	R1	Formula
321165	OH	C ₁₀ H ₁₁ NO
321166	(CH ₂) ₈ OH	C ₁₈ H ₂₇ NO
321167	(CH ₂) ₉ OH	C ₁₉ H ₂₉ NO

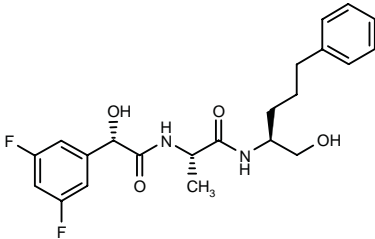
SOURCE – Meiji Milk Products.

REFERENCES

1. Ban, R. et al. (Meiji Milk Products Co., Ltd.) *Indole long chain alcohols and medicines containing them*. JP 2002114763.

321226

*N*²-[2(*S*)-(3,5-Difluorophenyl)-2-hydroxyacetyl]-*N*¹-[1(*S*)-(hydroxymethyl)-4-phenylbutyl]-L-alaninamide



C22 H26 F2 N2 O4; Mol wt: 420.4534

ACTION – β-Amyloid (Aβ) peptide inhibitor (EC₅₀ = 0.13 μM in HEK293 cells expressing amyloid precursor protein APP751), potentially useful for the treatment of Alzheimer's disease.

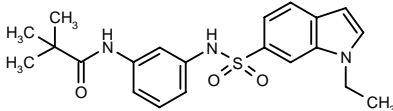
SOURCES – Elan; Lilly.

REFERENCES

1. Garofalo, A.W. et al. A series of C-terminal amino alcohol dipeptide Aβ inhibitors. 28th Natl Med Chem Symp (June 8-12, San Diego) 2002, Abst 11.

321323

N-[3-(1-Ethyl-1*H*-indol-6-ylsulfonamido)phenyl]-2,2-dimethylpropionamide



C21 H25 N3 O3 S; Mol wt: 399.5125

ACTION – A representative compound from a series of *N*-phenylsulfonamide derivatives that act as antagonists at 5-HT₆ receptors. In binding assays, it displayed a K_i value of 12 nM at 5-HT₆ receptors expressed in HEK293 cells. Potentially useful for the treatment of cognitive disorders, particularly Alzheimer’s disease and other dementias.

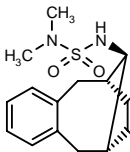
SOURCE – Bayer.

REFERENCES

1. Böss, F.-G. et al. (Bayer AG) Sulphonamides for the treatment of central nervous system diseases. DE 10053813, WO 0236115.

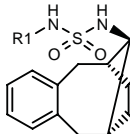
321437

syn-*N*-(5,6,7,8,9,10-Hexahydro-6,9-methanobenzo-cycloocten-11-yl)-*N*′, *N*′-dimethylsulfamide

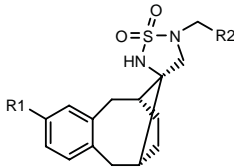


C15 H22 N2 O2 S; Mol wt: 294.4168

ACTION – Inhibitor of γ-secretase, potentially useful for the treatment of Alzheimer’s disease. Other exemplified sulfamides include the following:



Compound	R1	Formula
321438	cyclobutyl	C ₁₇ H ₂₄ N ₂ O ₂ S
321439	CH ₂ CF ₃	C ₁₅ H ₁₉ F ₃ N ₂ O ₂ S



Compound	R1	R2	Formula
321441	4-F-PhOCH ₂ CH ₂ O	Et	C ₂₅ H ₃₁ FN ₂ O ₄ S
321442	H	cyclopentyl	C ₂₀ H ₂₈ N ₂ O ₂ S
321443	4-CF ₃ -1-Pip-CH ₂ CH=CH	CF ₃	C ₂₅ H ₃₁ F ₆ N ₃ O ₂ S
321444	CH=NOH	CF ₃	C ₁₇ H ₂₀ F ₃ N ₃ O ₃ S
321445	3-THF-N(Me)CH ₂ CH=CH	CF ₃	C ₂₄ H ₃₂ F ₃ N ₃ O ₃ S
321446	3-(2-Pyr)-1,2,4-oxadiazol-5-yl	Et	C ₂₄ H ₂₇ N ₅ O ₃ S

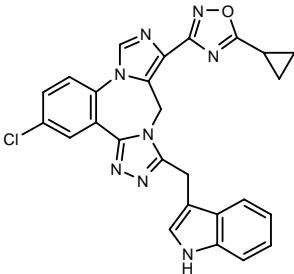
SOURCE – Merck Sharp & Dohme.

REFERENCES

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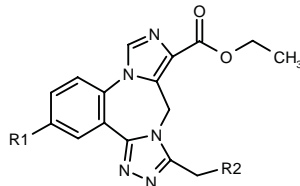
321724

3-Chloro-10-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-7-(1*H*-indol-3-ylmethyl)-9*H*-imidazo[1,5-*a*][1,2,4]triazolo[4,3-*d*]-[1,4]benzodiazepine



C26 H19 Cl N8 O; Mol wt: 494.9441

ACTION – A compound with affinity and selectivity for the α5 subunit of GABA_A receptors, potentially useful for the treatment of cognitive disorders, particularly Alzheimer’s disease. In radioligand binding assays using SF9 cells transfected with GABA_A receptors, it gave a K_i value of 1.3 nM at the α5 subunit, and exhibited 51-, 40- and 14-fold selectivity, respectively, over the α1, α2 and α3 subunits. Other exemplified benzodiazepine derivatives are:



Compound	R1	R2	Formula
321728	OMe	H	C ₁₇ H ₁₇ N ₅ O ₃
321729	OMe	3-indolyl	C ₂₅ H ₂₂ N ₆ O ₃
321730	Br	3-indolyl	C ₂₄ H ₁₉ BrN ₆ O ₂
321731	Br	3-MeO-Ph	C ₂₃ H ₂₀ BrN ₅ O ₃
321732	Cl	4-Pyr	C ₂₁ H ₁₇ ClN ₆ O ₂

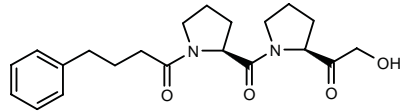
SOURCE – Roche.

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321947

N-(4-Phenylbutanoyl)-L-prolyl-L-prolyl-methanol



C21 H28 N2 O4; Mol wt: 372.4622

ACTION – Prolyl oligopeptidase (POP, also prolyl endopeptidase) inhibitor (IC₅₀ = 0.2 nM in pig brain), potentially useful for the treatment of Alzheimer’s disease.

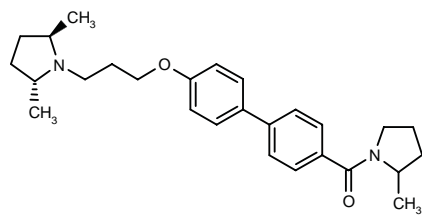
SOURCE – Finncoverly.

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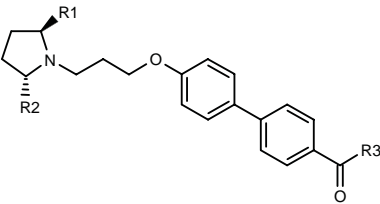
322090

1-[4’-[3-[2(R),5(R)-Dimethylpyrrolidin-1-yl]propoxy]-biphenyl-4-yl]-1-(2-methylpyrrolidin-1-yl)methanone

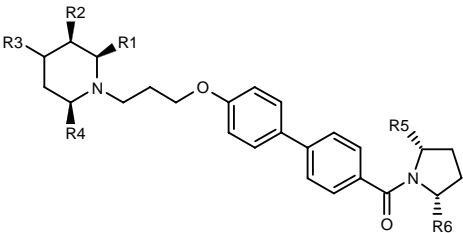


C27 H36 N2 O2; Mol wt: 420.5934

ACTION – Agent with affinity for histamine H₃ receptors, as demonstrated in rat brain preparations (K_i = 1.00 nM). Potentially useful for the treatment of Alzheimer’s disease, attention deficit hyperactivity disorder, epilepsy and schizophrenia. Further applications include acute myocardial infarction, asthma, cutaneous carcinoma, depression, inflammation, medullary thyroid carcinoma, melanoma, Ménière’s disease, migraine, motion sickness, obesity, pain, Parkinson’s disease and septic shock. Other exemplified aminoalkoxybiphenyl carboxamides include the following:



Compound	R1	R2	R3	Formula
322091	Me	Me	i-PrNH	C ₂₅ H ₃₄ N ₂ O ₂
322092	Me	Me	N(Et)2	C ₂₆ H ₃₆ N ₂ O ₂
322093	Me	Me	2(R),5(R)-(Me)2-1-pyrrolidinyl	C ₂₈ H ₃₈ N ₂ O ₂
322095	Me	Me	4-Me-1-Pip	C ₂₈ H ₃₈ N ₂ O ₂
322096	Me	Me	4-morpholinyl	C ₂₆ H ₃₄ N ₂ O ₃
322097	H	CH2OH	1-pyrrolidinyl	C ₂₅ H ₃₂ N ₂ O ₃



Compound	R1	R2	R3	R4	R5	R6	Formula
322094	H	H	Me	H	Me	Me	C ₂₈ H ₃₈ N ₂ O ₂
322098	Me	H	H	Me	H	H	C ₂₇ H ₃₆ N ₂ O ₂
322099	H	OH	H	H	H	H	C ₂₅ H ₃₂ N ₂ O ₃

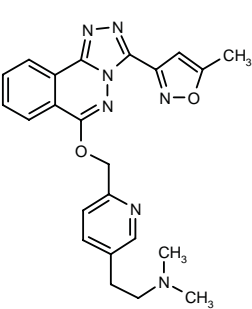
SOURCE – Abbott.

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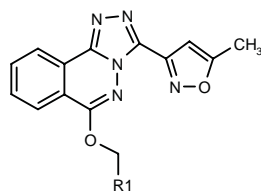
322206

N,N-Dimethyl-2-[6-[3-(5-methylisoxazol-3-yl)[1,2,4]-triazolo[3,4-a]phthalazin-6-yloxymethyl]pyridin-3-yl]ethylamine



C23 H23 N7 O2; Mol wt: 429.4817

ACTION – Agent with affinity for the α5 subunit of GABA_A receptors, potentially useful for the treatment of cognition disorders associated with Alzheimer’s disease, Parkinson’s disease, traumatic injury, stroke and Down’s syndrome, age-related memory deficits and attention deficit disorder. Other exemplified [1,2,4]triazolo[3,4-a]-phthalazine derivatives include the following:



Compound	R1	Formula
322209	6-[1-azetidinyI-CH2CH(OH)]-3-Pyr	C ₂₄ H ₂₃ N ₇ O ₃
322211	6-(1-imidazolyl-CH2CH2)-2-Pyr	C ₂₄ H ₂₀ N ₆ O ₂
322213	6-(1-Piz-CH2CH2)-3-Pyr	C ₂₅ H ₂₆ N ₆ O ₂
322214	6-(1-imidazolyl-CH2)-2-Pyr	C ₂₃ H ₁₈ N ₆ O ₂
322215	1-(NH2CH2CH2)-[1,2,4]-triazol-5-yl	C ₁₈ H ₁₇ N ₉ O ₂
322216	5-(1-pyrrolidinyl-CH2)-2-Pyr	C ₂₄ H ₂₃ N ₇ O ₂
322217	5-(t-BuNHCH2)-2-Pyr	C ₂₄ H ₂₅ N ₇ O ₂
322218	5-(CO2HCH2NHCH2)-2-Pyr	C ₂₂ H ₁₉ N ₇ O ₄

SOURCE – Merck Sharp & Dohme.

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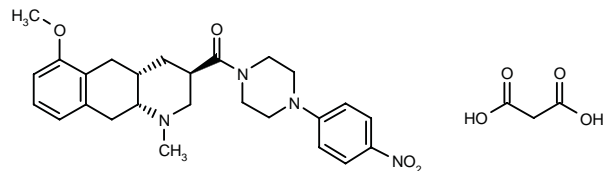
1. Chambers, M.S. et al. (Merck Sharp & Dohme Ltd.) *Nitrogen substd. 1,2,4-triazolo-[3,4-a]phthalazine derivs. for enhancing cognition*. WO 0242305.

NVP-SRA-880*

248195

1-[(3*R*,4*aR*,10*aR*)-6-Methoxy-1-methyl-1,2,3,4,4*a*,5,10,10*a*-octahydrobenzo[*g*]quinolin-3-yl)-1-[4-(4-nitrophenyl)-piperazin-1-yl]methanone malonate

SRA-880



C26 H32 N4 O4 . C3 H4 O4; Mol wt: 568.6234

ACTION – Somatostatin sst₁ receptor antagonist with high affinity for human, rat and mouse sst₁ receptors (pK_d = 8.0-8.2) and good, oral bioavailability and brain penetration. *In vivo*, compound (0.01-30 mg/kg p.o.) reduced aggressive behavior in rats and mice, while being inactive in tests predictive for anxiolytic and anti-depressant activity. It also improved performance in both step-down and step-through passive avoidance tests and improved short-term memory in an object recognition test in rats. No motor impairment or sedation were observed at pharmacologically active doses. Potentially useful for the treatment of cognition deficits and psychiatric disorders.

SOURCE – Novartis.

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1. Neumann, P. et al. (Novartis AG;Novartis Deutschland GmbH) *Benzo[*g*]quinoline derivs.* EP 0839136, JP 1999509197, US 5885988, WO 9703054.

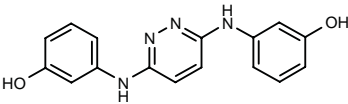
2. Daniel, H. *NVP-SRA880, a somatostatin sst1 receptor antagonist promotes social interactions, reduces aggressive behaviour and stimulates learning.* Pharmacologist 2002, 44(2, Suppl. 1): Abst 142.9.

*Identified compound **248195** Drug Data Rep 1997, 019(05): 0402.

RS-0406

322053

3,3'-(Pyridazin-3,6-diyl)bis(imino)bis(phenol)



C16 H14 N4 O2; Mol wt: 294.3126

ACTION – β -Sheet breaker able to significantly inhibit β -amyloid peptide (A β)-induced fibrillogenesis and to subsequently disassemble preformed fibrils *in vitro*. Compound improved A β -induced cytotoxicity in hippocampal neurons and A β -induced impairment of long-term potentiation in hippocampal slices. Potentially useful for the treatment of Alzheimer’s disease.

SOURCE – Sankyo.

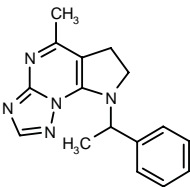
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RS-1178

322054

5-Methyl-8-(1-phenylethyl)-7,8-dihydro-6*H*-pyrrolo[3,2-*e*]-[1,2,4]triazolo[1,5-*a*]pyrimidine



C16 H17 N5; Mol wt: 279.3453

ACTION – Neuroprotective agent able to selectively inhibit β -amyloid peptide (A β)-induced macrophage activation, while having no effect against zymosan A- or lipopoly-saccharide-induced macrophage activation. It also inhibited neurotoxicity mediated by A β -induced macrophage activation, inhibited A β -induced inducible nitric oxide synthase (iNOS) expression in macrophages and reduced A β -induced ERK1/2 phosphorylation. Compound did not inhibit A β fibril formation, indicating that its effect may not be due to direct interference with A β . Potentially useful for the treatment of Alzheimer’s disease.

SOURCE – Sankyo.

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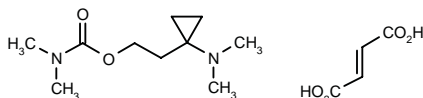
3. Sato, Y. et al. *Studies on cardiovascular agents. 6. Synthesis and coronary vasodilating and antihypertensive activities of 1,2,4-triazolo[1,5-a]pyrimidines fused to heterocyclic systems.* J Med Chem 1980, 23(8): 927.

4. Uryu, S. et al. *A novel compound, RS-1178, specifically inhibits neuronal cell death mediated by β -amyloid-induced macrophage activation in vitro.* Pharmacologist 2002, 44(2, Suppl. 1): Abst 67.6.

S-35836-1

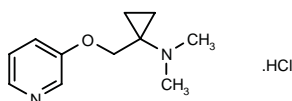
322125

N,N-Dimethylcarbamic acid 2-[1-(dimethylamino)cyclopropyl]ethyl ester fumarate



C10 H20 N2 O2 . C4 H4 O4; Mol wt: 316.3516

ACTION – Conformationally restricted acetylcholine analogue, a selective central nicotinic acetylcholine receptor $\alpha 4\beta 2$ ligand. Compound exhibited cognition-enhancing and analgesic properties in rodent models similar to those of (–)-nicotine. Potentially useful for the treatment of age-related cognitive disorders. Another related compound is:



S-35684-1 [322126]: C11 H16 N2 O . HCl

SOURCE – Servier.

REFERENCES

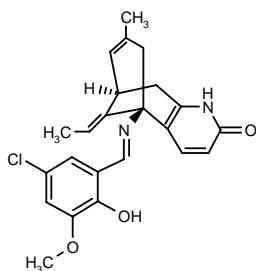
1. Goldstein, S. et al. (Servier Laboratoires) *1,1- And 1,2-disubst. cyclopropanes, process for their preparation and pharmaceutical compsns. thereof.* EP 1170281, FR 2810664, JP 2002069046.

2. Goldstein, S. et al. *Pharmacological characterization of novel conformationally restricted acetylcholine analogues as selective central nicotinic receptors ligands.* Pharmacologist 2002, 44(2, Suppl. 1): Abst 63.10.

ZT-1

321347

(5*R*,9*R*)-5-(5-Chloro-2-hydroxy-3-methoxybenzylidene-amino)-11-ethylidene-7-methyl-1,2,5,6,9,10-hexahydro-5,9-methanocycloocta[*b*]pyridin-2-one



C23 H23 Cl N2 O3; Mol wt: 410.8987

ACTION – Potent and selective inhibitor of acetylcholinesterase (AChE) with IC_{50} values of 64 nM and 116 μ M for inhibition of rat cortex AChE and rat serum butyrylcholinesterase (BuChE), a derivative of huperzine A with comparable potency against AChE but improved selectivity over BuChE. *In vivo* in mice, rats and monkeys, it was almost equipotent with huperzine A and more effective than donepezil and tacrine. Potentially useful for the treatment of Alzheimer's disease.

SOURCES – Debiopharm; H3 Pharma; Shanghai Institute Materia Medica, Shanghai (CN).

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1. Zhu, D. et al. (Tsumura & Co.;Shanghai Institute Materia Medica) *Huperzine A derivs., their preparation and their use.* EP 0806416, JP 1998511651, US 5929084, WO 9620176.

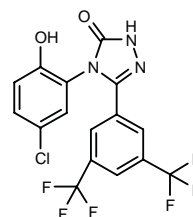
2. *ZT-1 tested in first-in-man trials.* DailyDrugNews.com (Daily Essentials) 2002, June 25.

3. *Product Portfolio.* H3 Pharma Inc. Web site.

TREATMENT OF CEREBROVASCULAR DISEASES

320818

5-[3,5-Bis(trifluoromethyl)phenyl]-4-(5-chloro-2-hydroxyphenyl)-3,4-dihydro-2*H*-1,2,4-triazol-3-one



C16 H8 Cl F6 N3 O2; Mol wt: 423.6992

ACTION – Large-conductance Ca^{2+} -activated potassium channel (maxi-K) opener (158% at 20 μ M) able to produce concentration-dependent increases in maxi-K current with an EC_{50} value of 43 μ M. Potentially useful for the treatment of stroke.

SOURCE – Bristol-Myers Squibb.

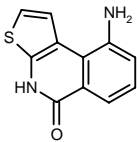
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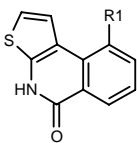
321237

9-Aminothieno[2,3-*c*]isoquinolin-5(4*H*)-one



C11 H8 N2 O S; Mol wt: 216.2632

ACTION – An inhibitor of poly(ADP-ribose)polymerase (PARP, NAD⁺ ADP-ribosyltransferase; IC₅₀ = 0.05 μM against PARP from calf fetal thymus) with potential in the treatment of ischemia–reperfusion injury, degenerative diseases, inflammatory disorders, cancer, leukemia and sarcoma. Other exemplified compounds are:



Compound	R1	Formula
321241	H	C ₁₁ H ₇ NOS
321243	OH	C ₁₁ H ₇ NO ₂ S
321244	OMe	C ₁₂ H ₉ NO ₂ S

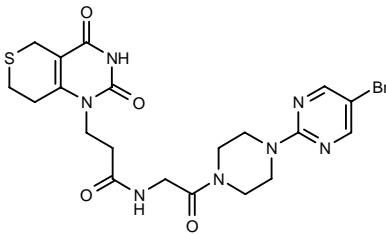
SOURCE – GlaxoSmithKline.

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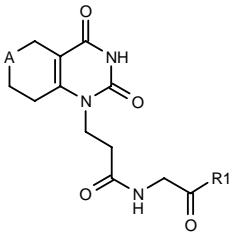
321862

N-[2-[4-(5-Bromopyrimidin-2-yl)piperazin-1-yl]-2-oxoethyl]-3-(2,4-dioxo-2,3,4,5,7,8-hexahydro-1*H*-thiopyrano[4,3-*d*]pyrimidin-1-yl)propionamide



C20 H24 Br N7 O4 S; Mol wt: 538.4246

ACTION – An inhibitor of poly(ADP-ribose)polymerase (PARP, NAD⁺ ADP-ribosyltransferase) with potential in the treatment of ischemia–reperfusion injury. It was shown to protect endothelial cells from hydrogen peroxide-induced cytotoxicity with an EC₅₀ of 0.02 μM. Other exemplified substituted amidoalkyl uracils are:



Compound	R1	A	Formula
321873	4-(4-Pyr)-Ph	CH2	C ₂₄ H ₂₄ N ₄ O ₄
321874	4-(1,3-benzodioxol-5-yl)-Ph	S	C ₂₆ H ₂₃ N ₃ O ₆ S
321875	4-(7-Me-thieno[3,2- <i>d</i>]pyrimidin-4-yl)-1-Piz	S	C ₂₃ H ₂₇ N ₇ O ₄ S ₂
321876	4-(2-pyrazinyl)-Ph	S	C ₂₂ H ₂₁ N ₅ O ₄ S
322135	4-(5-F-2-pyrimidinyl)-1-Piz	CH2	C ₂₁ H ₂₆ FN ₇ O ₄

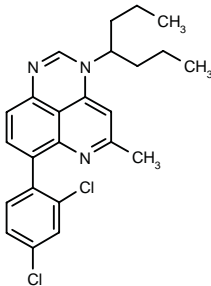
SOURCE – Bayer.

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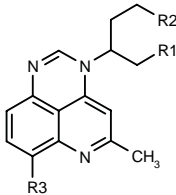
322020

7-(2,4-Dichlorophenyl)-5-methyl-3-(1-propylbutyl)-3*H*-pyrido[4,3-*de*]quinazoline



C24 H25 Cl2 N3; Mol wt: 426.3885

ACTION – Corticotropin-releasing factor (CRF) receptor antagonist with potential application in the treatment of stroke, anxiety, depression and irritable bowel syndrome. Other exemplified compounds include the following:



Compound	R1	R2	R3	Formula
322021	Me	H	2,4-(Cl)2-Ph	C ₂₂ H ₂₁ Cl ₂ N ₃
322022	Et	Me	4-Cl-Ph	C ₂₄ H ₂₆ ClN ₃
322023	Et	Me	2-benzofuryl	C ₂₆ H ₂₇ N ₃ O
322024	Et	Me	2-benzothienyl	C ₂₆ H ₂₇ N ₃ S
322025	Et	Me	2-MeO-5- <i>i</i> -Pr-Ph	C ₂₈ H ₃₆ N ₃ O
322026	Et	Me	3-CF3-Ph	C ₂₅ H ₂₆ F ₃ N ₃
322028	Et	Me	4-(CF3O)-Ph	C ₂₅ H ₂₆ F ₃ N ₃ O
322029	-CH(Me)CH2-		2,4-(Cl)2-Ph	C ₂₄ H ₂₃ Cl ₂ N ₃

SOURCE – Neurocrine Biosciences.

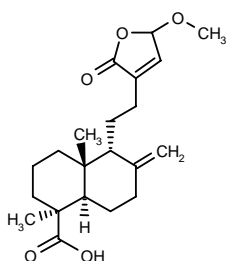
REFERENCES

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15-METHOXYPINUSOLIDIC ACID

321257

(1*S*,4*aR*,5*R*,8*aR*)-5-[2-(5-Methoxy-2-oxo-2,5-dihydrofuran-3-yl)ethyl]-1,4*a*-dimethyl-6-methylenedecahydronaphthalene-1-carboxylic acid



C21 H30 O5; Mol wt: 362.4630

ACTION – Neuroprotective agent, a pinusolide derivative isolated from the leaves of *Biota orientalis* able to significantly attenuate neuronal cell death induced by glutamate in primary cultures of rat cortical cells.

SOURCE – Seoul National University, Seoul (KR).

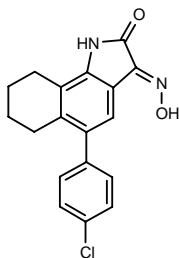
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NS-1231

310282

5-(4-Chlorophenyl)-2,3,6,7,8,9-hexahydro-1*H*-benzo[*g*]indole-2,3-dione 3-oxime



C18 H15 Cl N2 O2 ; Mol wt: 363.2424

ACTION – Neurotrophic agent able to rescue nerve growth factor (NGF)-differentiated PC-12 cells and neurites from death induced by withdrawal of trophic factors and to enhance the survival of tyrosine hydroxylase-positive mesencephalic neurons. In a gerbil model of transient global cerebral ischemia, compound (10-15 mg/kg i.p.) given after an ischemic insult significantly reduced hippocampal CA1 neuronal loss; the highest dose produced 43% reduction in total infarct volume. Potentially useful for the treatment of stroke.

SOURCES – NeuroSearch; NsGene.

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2. Dago, L. et al. *NS 1231, a novel compound with neurotrophic-like effects in vitro and in vivo*. J Neurochem 2002, 81(1): 17.
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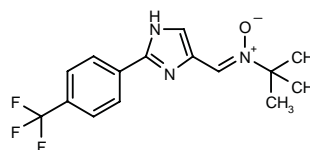
S-34176-1

322055

N-*tert*-Butyl-*N*-[(*Z*)-2-[4-(trifluoromethyl)phenyl]-1*H*-imidazol-4-ylmethylene]amine *N*-oxide

N-*tert*-Butyl- α -[2-[4-(trifluoromethyl)phenyl]-1*H*-imidazol-4-yl]nitron

S-34176



C15 H16 F3 N3 O; Mol wt: 311.3054

ACTION – Neuroprotective spin-trapping agent with radical-scavenging activity. Compound was effective in a model of kainic acid-induced hippocampal neuronal death in rats and *t*-butylhydroperoxide-induced lethality in mice, where it compared favorably with the reference compound *tert*-butylphenylnitron (*t*-BPN). S-34176-1 was able to prevent the striatal dopamine depletion induced by *d*-methamphetamine in mice. Potentially useful for the treatment of oxidative stress-related CNS disorders.

SOURCE – Servier.

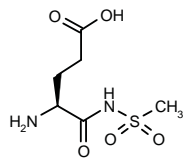
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SYM-2061

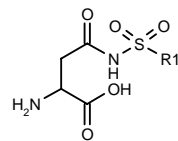
322179

N¹-(Methylsulfonyl)-L-α-glutamine



C6 H12 N2 O5 S; Mol wt: 224.2358

ACTION – High-affinity ligand for the glutamate transporter EAAT1-5 (K_i = 14 and 16 nM for displacement of [³H]-4-methylglutamate and [³H]-D-aspartate binding, respectively), potentially useful for the treatment of stroke. Other related compounds are:



Compound	R1	Isomer	Formula
SYM-2062 [322180]	Me	R	C ₉ H ₁₀ N ₂ O ₅ S
SYM-2064 [322181]	CF3	S	C ₈ H ₇ F ₃ N ₂ O ₅ S

SOURCES – Monash University, Clayton (AU); Transgenomics.

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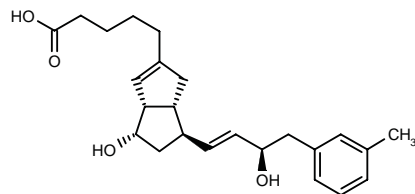
2. Maccocchini, M.-L. and Pei, X.-F. (Transgenomics, Inc.) *Method for modulation, stimulation, and inhibition of glutamate reuptake*. WO 0240002.

3. Beart, P.M. et al. *Novel insights into the structure-activity requirements of glutamate transporters from binding studies with [³H](2S,4R)-4-methylglutamate, [³H]D-aspartate and 4-methylglutamate analogs*. Pharmacologist 2002, 44(2, Suppl. 1): Abst 138.1.

MISCELLANEOUS NEUROLOGIC DRUGS

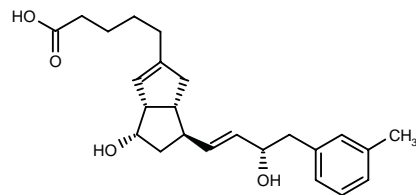
321151

5-[(3a*S*,4*S*,6*R*,6a*R*)-4-Hydroxy-6-[3(*R*)-hydroxy-4-(3-methylphenyl)-1-butenyl]-1,3a,4,5,6,6a-hexahydro-pentalen-2-yl]pentanoic acid



C24 H32 O4; Mol wt: 384.5128

ACTION – Agent that selectively binds to CNS prostacyclin receptors, while showing weak affinity for peripheral nervous system receptors. Compound concentration-dependently inhibited [³H]-isocarbacyclin binding to receptors in rat brain preparations, while it inhibited ADP-induced platelet aggregation in rat blood with an IC₅₀ > 400 nM. The compound is expected to be useful for the treatment of CNS disorders, as well as for the study of prostacyclin receptors. Another exemplified compound is:



321152: C24 H32 O4

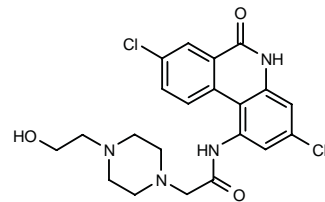
SOURCE – Japan Science and Technology.

REFERENCES

1. Watanabe, K. et al. (Japan Science and Technology Corp.) *Isocarbacyclin derivs*. JP 2002128730.

321153

N-(3,8-Dichloro-6-oxo-5,6-dihydrophenanthridin-1-yl)-2-[4-(2-hydroxyethyl)piperazin-1-yl]acetamide



C21 H22 Cl2 N4 O3; Mol wt: 449.3358

ACTION – A representative compound from a series of phenanthridine derivatives with the ability to potentiate the effect of neurotrophin. This compound was shown to enhance the activity of neurotrophin-3 (NT-3) in cholinergic nerve cells from rat fetal brain preparations and is reportedly useful for the treatment of neuropathy.

SOURCE – Sankyo.

REFERENCES

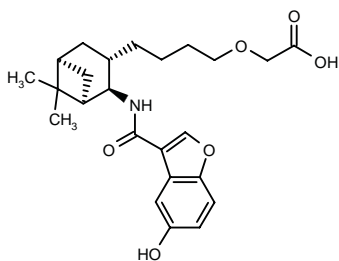
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RESPIRATORY DRUGS

TREATMENT OF UPPER
RESPIRATORY TRACT DISORDERS

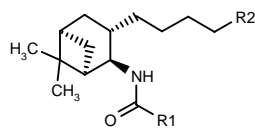
321559

2-[4-[(1*R*,2*R*,3*S*,5*S*)-2-(5-Hydroxy-1-benzofuran-3-ylcarboxamido)-6,6-dimethylbicyclo[3.1.1]hept-3-yl]-butoxy]acetic acid



C24 H31 N O6; Mol wt: 429.5099

ACTION – A metabolically stable prostaglandin PGD₂ (DP) receptor antagonist with an IC₅₀ of 0.0035 μM for inhibition of [³H]-PGD₂ binding to its receptors in human platelet membranes, and also able to antagonize the PGD₂-induced increase in cAMP levels (IC₅₀ = 0.0082 μM). When administered to rats at doses of 0.5-10 mg/kg i.v., compound had a plasma half-life of 23.4 min. Potentially useful for the treatment of nasal obstruction, allergic conjunctivitis and allergic rhinitis, among other disorders associated with PGD₂ overproduction. Other exemplified compounds include the following:



Compound	R1	R2	Formula
321560	3-thienyl	CH=CHCO2H	C ₂₁ H ₂₉ NO ₃ S
321561	3-thienyl	OCH2CO2H	C ₂₀ H ₂₉ NO ₄ S
321562	3-thienyl	SCH2CO2H	C ₂₀ H ₂₉ NO ₃ S ₂
321563	7-benzothienyl	CH=CHCO2H	C ₂₅ H ₃₁ NO ₃ S
321564	7-benzothienyl	OCH2CO2H	C ₂₄ H ₃₁ NO ₄ S
321565	5-OH-3-benzofuryl	CH=CHCO2H	C ₂₅ H ₃₁ NO ₅

SOURCE – Shionogi.

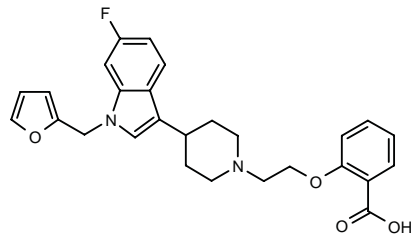
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ASTHMA THERAPY

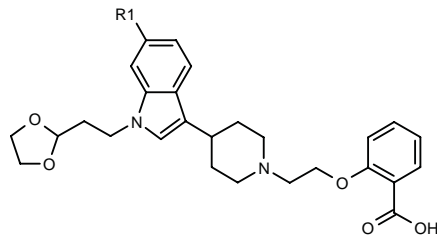
321245

2-[2-[4-[6-Fluoro-1-(furan-2-ylmethyl)-1*H*-indol-3-yl]piperidin-1-yl]ethoxy]benzoic acid

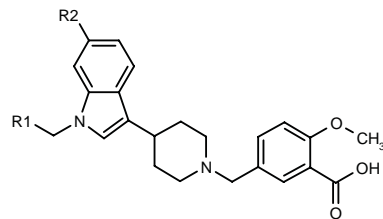


C27 H27 F N2 O4; Mol wt: 462.5183

ACTION – Antihistaminic agent that gave an IC₅₀ of 37 nM at histamine H₁ receptors in binding assays. When orally administered to rats at 1 mg/kg, compound inhibited histamine-induced skin permeability by > 50%. Reported to be devoid of effects on blood pressure and heart rate, and to be unable to penetrate the blood–brain barrier. Potentially useful for the treatment of allergic disorders including bronchial asthma, rhinitis, conjunctivitis, dermatitis and urticaria. Other exemplified indolylpiperidine derivatives are:



Compound	R1	Formula
321246	H	C ₂₇ H ₃₂ N ₂ O ₅
321247	F	C ₂₇ H ₃₁ FN ₂ O ₅



Compound	R1	R2	Formula
321248	2-thienyl	H	C ₂₇ H ₂₈ N ₂ O ₃ S
321249	3-thienyl-CH2	H	C ₂₈ H ₃₀ N ₂ O ₃ S
321250	3-thienyl-CH2	F	C ₂₈ H ₂₉ FN ₂ O ₃ S
321251	5-Cl-2-thienyl	F	C ₂₇ H ₂₆ ClFN ₂ O ₃ S
321252	3-furyl	F	C ₂₇ H ₂₇ FN ₂ O ₄
321253	2-thienyl	F	C ₂₇ H ₂₇ FN ₂ O ₃ S
321254	2-furyl	H	C ₂₇ H ₂₈ N ₂ O ₄
321255	3-furyl	H	C ₂₇ H ₂₈ N ₂ O ₄

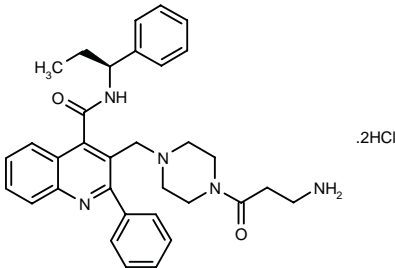
SOURCE – Almirall Prodesfarma.

REFERENCES

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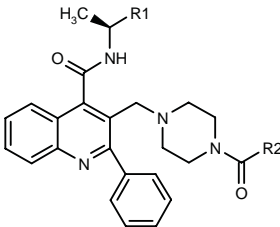
321270

(-)-3-[4-(3-Aminopropionyl)piperazin-1-ylmethyl]-2-phenyl-N-[1(S)-phenylpropyl]quinoline-4-carboxamide dihydrochloride



C33 H37 N5 O2 . 2HCl; Mol wt: 608.6101

ACTION – Tachykinin NK₂ and/or NK₃ receptor antagonist, potentially useful for the treatment of a broad range of disorders including chronic obstructive pulmonary disease, asthma, cough, inflammation, psoriasis, arthritis, pain, allergy, ophthalmic diseases, skin disorders, transplant rejection, systemic lupus erythematosus, ulcerative colitis, Crohn’s disease, urinary incontinence, CNS disorders, multiple sclerosis, etc. Other exemplified quinoline derivatives are:



Compound	R1	R2	Formula
321274	Ph	1-(CO2HCH2)-cyclopentyl-CH2	C ₃₆ H ₄₂ N ₄ O ₄
321275	Ph	CH2C(Me)2CH2CO2H	C ₃₆ H ₄₀ N ₄ O ₄
321276	Ph	CH=CHCO2H	C ₃₃ H ₃₂ N ₄ O ₄
321277	cyclohexyl	3-CO2H-2-pyrazinyl	C ₃₅ H ₃₈ N ₆ O ₄
321278	cyclohexyl	4-CO2H-Ph	C ₃₇ H ₄₀ N ₄ O ₄
321279	cyclohexyl	H	C ₃₀ H ₃₆ N ₄ O ₂
321280	cyclohexyl	CH2CH2NH2	C ₃₂ H ₄₁ N ₅ O ₂
321281	cyclohexyl	1-Pip-CH2CH2	C ₃₇ H ₄₉ N ₅ O ₂

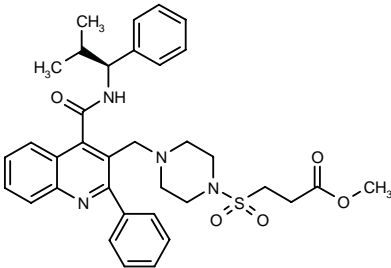
SOURCE – GlaxoSmithKline.

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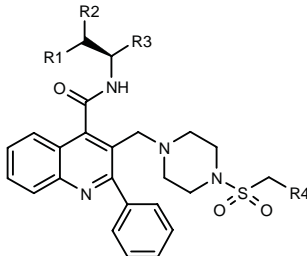
321282

3-[4-[4-[N-[2-Methyl-1(S)-phenylpropyl]carbamoyl]-2-phenylquinolin-3-ylmethyl]piperazin-1-ylsulfonyl]propionic acid methyl ester



C35 H40 N4 O5 S; Mol wt: 628.7900

ACTION – Tachykinin NK₂ and/or NK₃ receptor antagonist, potentially useful for the treatment of a broad range of disorders including chronic obstructive pulmonary disease, asthma, cough, inflammation, psoriasis, arthritis, pain, allergy, ophthalmic diseases, skin disorders, transplant rejection, systemic lupus erythematosus, ulcerative colitis, Crohn’s disease, urinary incontinence, CNS disorders, multiple sclerosis, etc. Other exemplified quinoline-4-carboxamide derivatives are:



Compound	R1	R2	R3	R4	Formula
321283	Me	Me	Ph	CH2CO2H	C ₃₄ H ₃₈ N ₄ O ₅ S
321284	H	Me	Ph	CH2N(Et)2	C ₃₆ H ₄₅ N ₅ O ₃ S
321285	H	H	cyclohexyl	H	C ₃₀ H ₃₈ N ₄ O ₃ S

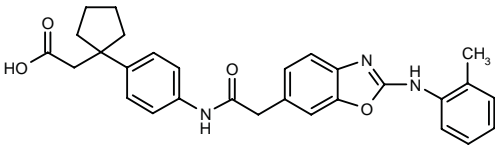
SOURCE – GlaxoSmithKline.

REFERENCES

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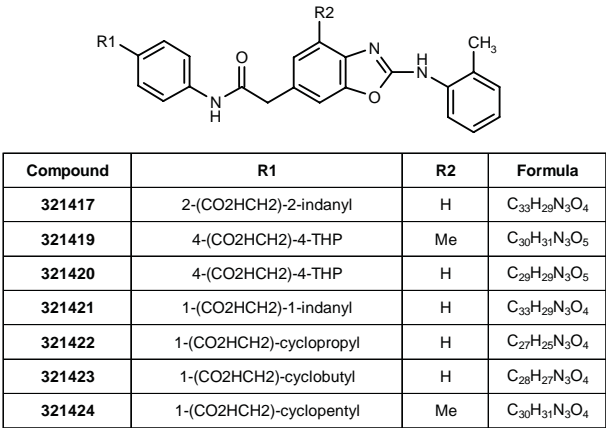
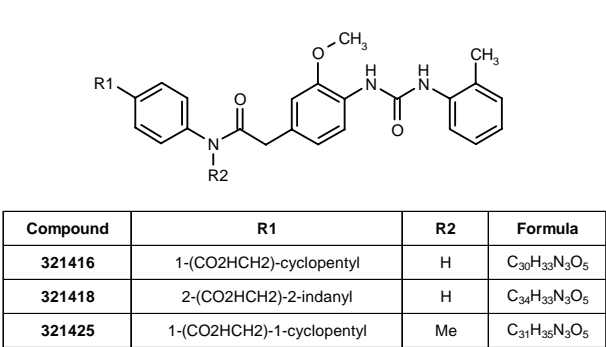
321414

2-[1-[4-[2-[2-(2-Methylphenylamino)benzoxazol-6-yl]-acetamido]phenyl]cyclopentyl]acetic acid



C29 H29 N3 O4; Mol wt: 483.5651

ACTION – Modulator of the interaction of VCAM-1 with the integrin $\alpha_4\beta_1$ (VLA-4) receptor, potentially useful for the treatment of inflammatory disorders, particularly asthma. Other specifically claimed substituted alkanoic acids are:



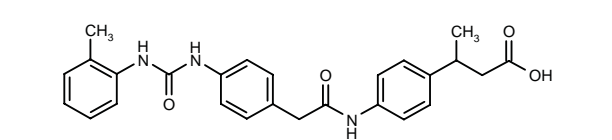
SOURCE – Aventis Pharma.

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321491

3-[4-[2-[4-[3-(2-Methylphenyl)ureido]phenyl]acetamido]-phenyl]butyric acid



C26 H27 N3 O4; Mol wt: 445.5163

ACTION – Integrin $\alpha_4\beta_1$ antagonist (IC₅₀ = 1.3 nM by binding affinity) able to inhibit by 48% the immediate phase of the antigen-induced bronchial response in a sheep model of allergic airways disease when given at a dose of 30 mg/kg 30 min before antigen challenge. It was also able to completely suppress the late-phase bronchoconstriction and the antigen-induced nonspecific airways hyperresponsiveness to inhaled carbachol. Potentially useful for the treatment of several inflammatory diseases such as asthma and rheumatoid arthritis.

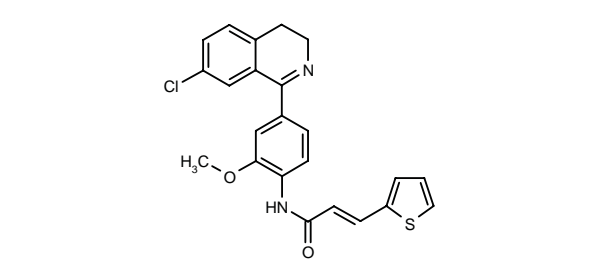
SOURCE – Biogen.

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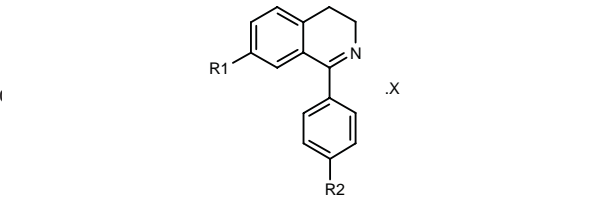
321810

N-[4-(7-Chloro-3,4-dihydroisoquinolin-1-yl)-2-methoxy-phenyl]-3-(2-thienyl)-2(E)-propenamide



C23 H19 Cl N2 O2 S; Mol wt: 422.9341

ACTION – Phosphodiesterase type 7 (PDE7) inhibitor with a –logIC₅₀ of 6.07 against PDE7 expressed in SF21 cells. Potentially useful for the treatment of inflammatory airways diseases such as bronchial asthma and chronic obstructive pulmonary disease. Other applications include psoriasis, atopic dermatitis, glomerulonephritis, auto-immune diabetes, multiple sclerosis, Crohn’s disease, ulcerative colitis, conjunctivitis, rheumatoid arthritis, transplant rejection, AIDS, T-cell leukemia and other tumors. Other exemplified 3,4-dihydroisoquinoline



Compound	R1	R2	X	Formula
321811	Cl	1-(CO2Me)-3-indolyl-CH2CH2NHCO		C ₂₈ H ₂₄ ClN ₃ O ₃
321812	Cl	CO2H	HCl	C ₁₆ H ₁₂ ClNO ₂ ·HCl
321813	F	4-Ac-PhNHCONH		C ₂₄ H ₂₀ FN ₃ O ₂

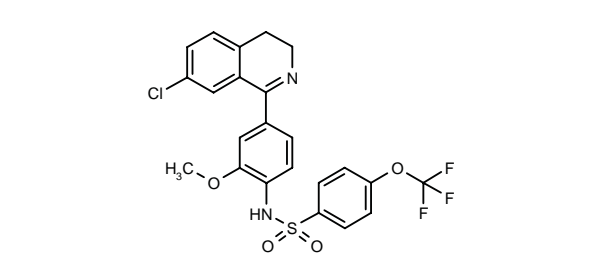
SOURCE – Altana Pharma.

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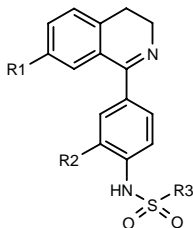
321814

N-[4-(7-Chloro-3,4-dihydroisoquinolin-1-yl)-2-methoxy-phenyl]-4-(trifluoromethoxy)benzenesulfonamide



C23 H18 Cl F3 N2 O4 S; Mol wt: 510.9182

ACTION – Phosphodiesterase type 7 (PDE7) inhibitor with a $-\log IC_{50}$ of 7.49 against PDE7 expressed in SF21 cells. Potentially useful for the treatment of inflammatory airways diseases such as bronchial asthma and chronic obstructive pulmonary disease. Other applications include psoriasis, atopic dermatitis, glomerulonephritis, autoimmune diabetes, multiple sclerosis, Crohn’s disease, ulcerative colitis, conjunctivitis, rheumatoid arthritis, transplant rejection, AIDS, T-cell leukemia and other tumors. Other exemplified 3,4-dihydroisoquinoline derivatives are:



Compound	R1	R2	R3	Formula
321815	Cl	OMe	4-Me-Ph	C ₂₃ H ₂₁ ClN ₂ O ₃ S
321816	H	OMe	5-(3-isoxazolyl)-2-thienyl	C ₂₃ H ₁₉ N ₃ O ₄ S ₂
321817	F	H	3-CF3-Ph	C ₂₂ H ₁₆ F ₄ N ₂ O ₂ S
321818	F	H	2-Naph	C ₂₅ H ₁₉ FN ₂ O ₂ S
321819	Cl	H	CH=CHPh	C ₂₃ H ₁₉ ClN ₂ O ₂ S
321820	Cl	H	4-Br-5-Cl-2-thienyl	C ₁₉ H ₁₃ BrCl ₂ N ₂ O ₂ S ₂

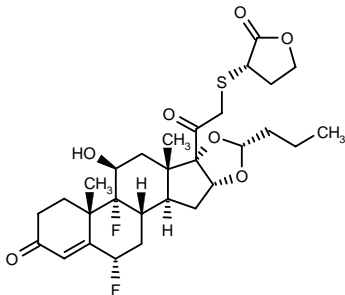
SOURCE – Altana Pharma.

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322129

16 α ,17 α -[(*R*)-Butylidenedioxy]-6 α ,9-difluoro-11 β -hydroxy-21-[2-oxotetrahydrofuran-3(*S*)-ylsulfanyl]pregn-4-ene-3,20-dione



C29 H38 F2 O7 S; Mol wt: 568.6742

ACTION – Lung-selective glucocorticoid antedrug with *in vitro* functional agonist activity comparable to that of dexamethasone. It was rapidly hydrolyzed in plasma by the enzyme paraoxonase. Potentially useful for the treatment of asthma.

SOURCE – GlaxoSmithKline.

REFERENCES

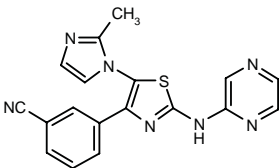
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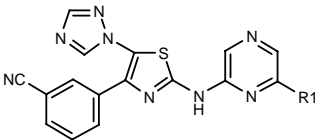
322136

3-[5-(2-Methyl-1*H*-imidazol-1-yl)-2-(pyrazin-2-ylamino)-thiazol-4-yl]benzonitrile



C18 H13 N7 S; Mol wt: 359.4157

ACTION – Adenosine A_{2B} and A₃ receptor antagonist with selectivity over A₁ and A_{2A} receptors, giving a K_b of 4 nM at A_{2B} receptors in a reporter gene assay and inhibiting A₃ receptor activation *in vitro* with a K_i of 10 nM. Potentially useful for the treatment of inflammatory or obstructive airways diseases. Other exemplified aminothiazoles are:



Compound	R1	Formula
322137	H	C ₁₆ H ₁₀ N ₈ S
322138	OCH2CH2OMe	C ₁₉ H ₁₆ N ₈ O ₂ S

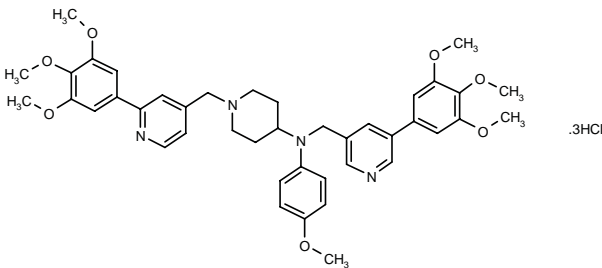
SOURCE – Novartis.

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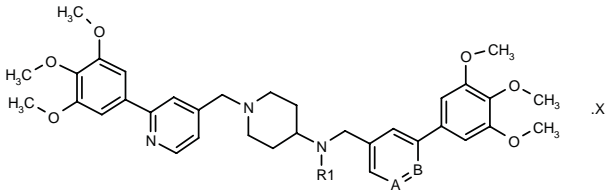
322239

N-(4-Methoxyphenyl)-1-[2-(3,4,5-trimethoxyphenyl)-pyridin-4-ylmethyl]-*N*-[5-(3,4,5-trimethoxyphenyl)pyridin-3-ylmethyl]piperidin-4-amine trihydrochloride

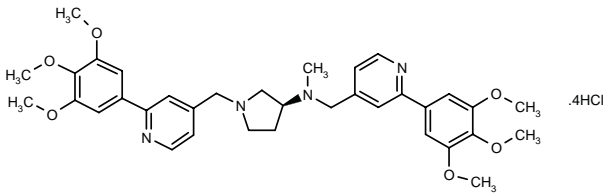


C42 H48 N4 O7 . 3HCl; Mol wt: 830.2449

ACTION – Cell adhesion inhibitor, proven to inhibit the TNF- α -stimulated adhesion of U-937 cells to human umbilical vein endothelial cell (HUVEC)-coated plates with an IC₅₀ of 0.03 μ M. Potentially useful for the treatment of allergy, asthma, inflammation, rheumatic diseases, arteriosclerosis and Sjögren's syndrome. Other exemplified compounds are:



Compound	R1	A	B	X	Formula
322241	H	CH	N	difumarate	C ₃₅ H ₄₂ N ₄ O ₆ ·2C ₄ H ₄ O ₄
322242	Me	N	CH	difumarate	C ₃₆ H ₄₄ N ₄ O ₆ ·2C ₄ H ₄ O ₄
322243	4-MeO-Ph	CH	N	3HCl	C ₄₂ H ₄₈ N ₄ O ₇ ·3HCl
322244	CH ₂ Ph	CH	N	4HCl	C ₄₂ H ₄₈ N ₄ O ₆ ·4HCl
322245	CH ₂ Ph	N	CH	4HCl	C ₄₂ H ₄₈ N ₄ O ₆ ·4HCl
322246	3,5-(MeO) ₂ -Ph	CH	N	3HCl	C ₄₃ H ₅₀ N ₄ O ₈ ·3HCl
322247	1,3-benzodioxol-5-yl	CH	N	3HCl	C ₄₂ H ₄₆ N ₄ O ₈ ·3HCl



322240: C35 H42 N4 O6 . 4HCl

SOURCE – Kowa.

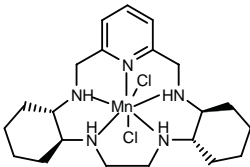
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M-40419

319700

Dichloro[(4a*S*,13a*S*,17a*S*,21a*S*)-11,7-nitrilo-2,3,4,4a,5,6,7,12,13,13a,14,15,16,17,17a,18,19,20,21,21a-eicosahydro-1*H*-dibenzo[*b,h*][1,4,7,10]tetraazacycloheptadecine- $\kappa N^5, \kappa N^{13}, \kappa N^{18}, \kappa N^{21}, \kappa N^{22}$]manganese



C21 H35 Cl2 Mn N5; Mol wt: 483.3865

ACTION – Low-molecular-weight superoxide dismutase (SOD) mimetic able to selectively remove superoxide anions and to attenuate hyperalgesia in models of acute inflammatory and chronic neuropathic pain. Moreover, in sensitized guinea pigs, compound (1 mg/kg i.p. before ovalbumin or 0.3 or 1.3 mg/ml by aerosol before or during ovalbumin challenge) prevented antigen-induced bronchoconstriction by reducing the severity of dyspnea, prolonging the latency to bronchospasm, reducing respiratory failure and alveolar dilatation, and blocking mast cell degranulation and neutrophil infiltration. Potentially useful for the treatment of asthma and anaphylactic reactions, and as an analgesic agent for the management of acute and chronic pain.

SOURCE – MetaPhore.

REFERENCES

1. Masini, E. *Prevention of antigen-induced bronchoconstriction by SOD mimetic compounds, M40403 and M40419, in actively sensitized guinea-pigs*. Pharmacologist 2002, 44(2, Suppl. 1): Abst 134.34.

2. Masini, E. et al. *Prevention of antigen-induced bronchoconstriction by M40419, a SOD mimetic compound, in actively sensitized guinea-pigs*. 31st Annu Meet Eur Histamine Res Soc (May 22-26, Eger) 2002, Abst O33.

3. Masini, E. et al. *Prevention of antigen-induced early obstructive reaction by inhaled M40419 in actively sensitized guinea pigs*. 98th Int Conf Am Thorac Soc (May 17-22, Atlanta) 2002, Abst 317.

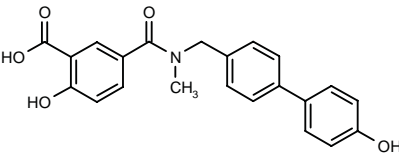
4. Salvemini, D. et al. *Superoxide anions play a critical role in the development of acute and chronic pain: Potential therapeutic use of superoxide dismutase mimetics*. Pharmacologist 2002, 44(2, Suppl. 1): Abst 37.4.

SP-727

322337

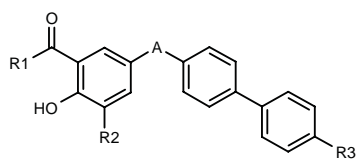
2-Hydroxy-5-[*N*-(4'-hydroxybiphenyl-4-ylmethyl)-*N*-methylcarbamoyl]benzoic acid

6-Hydroxy-*N*-(4'-hydroxybiphenyl-4-ylmethyl)-*N*-methylisophthalamic acid



C22 H19 N O5; Mol wt: 377.3941

ACTION – Inhibitor of IL-4 signaling claimed for use in the treatment of asthma, allergy, autoimmune diseases, osteoarthritis and rheumatoid arthritis. Other exemplified salicylic acid analogues are:



Compound	R1	R2	R3	A	Formula
SP-724 [322338]	OH	H	OH	-CONHCH2-	C ₂₁ H ₁₇ NO ₅
SP-821 [322430]	OH	H	OH	-CH2NHCO-	C ₂₁ H ₁₇ NO ₅
SP-2290 [322431]	OMe	OMe	H	-CH2NHCO-	C ₂₃ H ₂₁ NO ₅
SP-2341 [322432]	NHSO2CH2Ph	OMe	H	-CH2NHCO-	C ₂₉ H ₂₆ N ₂ O ₆ S
SP-549 [322433]	OH	H	OH	-(CH2)3-	C ₂₂ H ₂₀ O ₄
SP-477 [322434]	OH	H	OH	-(CH2)6-	C ₂₈ H ₂₆ O ₄
SP-478 [322435]	OH	H	OH	-CH=CHCH2- CH2CH=CH-	C ₂₈ H ₂₂ O ₄
SP-660 [322436]	OH	H	OH	-(CH2)5-	C ₂₄ H ₂₄ O ₄
SP-2293 [322438]	OH	OMe	H	-CH2NHCO-	C ₂₂ H ₁₉ NO ₅

SOURCE – Sunesis.

REFERENCES

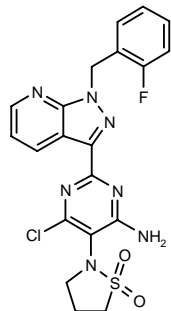
1. Barr, K.J. et al. (Sunesis Pharmaceuticals, Inc.) *Salicylate analogs as interleukin-4 antagonists*. WO 0244128.

CARDIOVASCULAR DRUGS

ANTIHYPERTENSIVE DRUGS

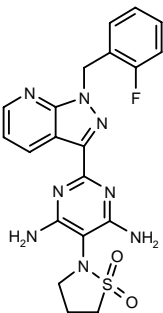
322248

6-Chloro-5-(1,1-dioxoisothiazolidin-2-yl)-2-[1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl]pyrimidin-4-amine



C20 H17 Cl F N7 O2 S; Mol wt: 473.9183

ACTION – Antihypertensive agent that activates soluble guanylate cyclase (sGC) and thereby increases cGMP levels. It was shown to inhibit phenylephrine-stimulated contractions in rabbit aortic preparations with an IC₅₀ of 290 nM. Potentially useful for the treatment of cardiovascular disorders, hypertonia, thromboembolic disorders, ischemia, sexual dysfunction, inflammation and CNS disorders. Another exemplified compound is:



322249: C20 H19 F N8 O2 S

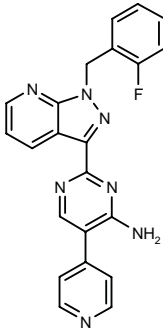
SOURCE – Bayer.

REFERENCES

1. Stasch, J.-P. et al. (Bayer AG) *Novel sulfonamide-substd. pyrazolopyridine derivs*. DE 10057754, WO 0242302.

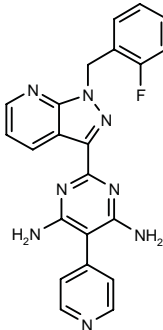
322250

2-[1-(2-Fluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl]-5-(4-pyridyl)pyrimidin-4-amine



C22 H16 F N7; Mol wt: 397.4154

ACTION – Antihypertensive agent that activates soluble guanylate cyclase (sGC) and thereby increases cGMP levels. It was shown to inhibit phenylephrine-stimulated contractions in rabbit aortic preparations with an IC₅₀ of 0.66 μM. Potentially useful for the treatment of cardiovascular disorders, hypertonia, thromboembolic disorders, ischemia, sexual dysfunction, inflammation and CNS disorders. Another exemplified compound is:

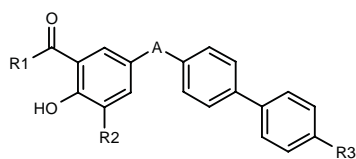


322251: C22 H17 F N8

SOURCE – Bayer.

REFERENCES

1. Stasch, J.-P. et al. (Bayer AG) *Novel pyridine-substd. pyrazolopyridine derivs*. WO 0242301.



Compound	R1	R2	R3	A	Formula
SP-724 [322338]	OH	H	OH	-CONHCH2-	C ₂₁ H ₁₇ NO ₅
SP-821 [322430]	OH	H	OH	-CH2NHCO-	C ₂₁ H ₁₇ NO ₅
SP-2290 [322431]	OMe	OMe	H	-CH2NHCO-	C ₂₃ H ₂₁ NO ₅
SP-2341 [322432]	NHSO2CH2Ph	OMe	H	-CH2NHCO-	C ₂₉ H ₂₆ N ₂ O ₆ S
SP-549 [322433]	OH	H	OH	-(CH2)3-	C ₂₂ H ₂₀ O ₄
SP-477 [322434]	OH	H	OH	-(CH2)6-	C ₂₅ H ₂₆ O ₄
SP-478 [322435]	OH	H	OH	-CH=CHCH2-CH2CH=CH-	C ₂₅ H ₂₂ O ₄
SP-660 [322436]	OH	H	OH	-(CH2)5-	C ₂₄ H ₂₄ O ₄
SP-2293 [322438]	OH	OMe	H	-CH2NHCO-	C ₂₂ H ₁₉ NO ₅

SOURCE – Sunesis.

REFERENCES

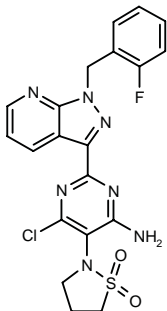
1. Barr, K.J. et al. (Sunesis Pharmaceuticals, Inc.) *Salicylate analogs as interleukin-4 antagonists*. WO 0244128.

CARDIOVASCULAR DRUGS

ANTIHYPERTENSIVE DRUGS

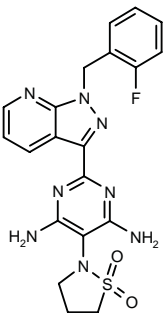
322248

6-Chloro-5-(1,1-dioxoisothiazolidin-2-yl)-2-[1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl]pyrimidin-4-amine



C20 H17 Cl F N7 O2 S; Mol wt: 473.9183

ACTION – Antihypertensive agent that activates soluble guanylate cyclase (sGC) and thereby increases cGMP levels. It was shown to inhibit phenylephrine-stimulated contractions in rabbit aortic preparations with an IC₅₀ of 290 nM. Potentially useful for the treatment of cardiovascular disorders, hypertonia, thromboembolic disorders, ischemia, sexual dysfunction, inflammation and CNS disorders. Another exemplified compound is:



322249: C20 H19 F N8 O2 S

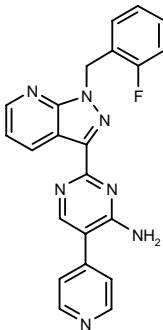
SOURCE – Bayer.

REFERENCES

1. Stasch, J.-P. et al. (Bayer AG) *Novel sulfonamide-substd. pyrazolopyridine derivs*. DE 10057754, WO 0242302.

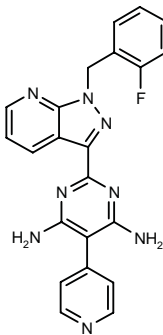
322250

2-[1-(2-Fluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl]-5-(4-pyridyl)pyrimidin-4-amine



C22 H16 F N7; Mol wt: 397.4154

ACTION – Antihypertensive agent that activates soluble guanylate cyclase (sGC) and thereby increases cGMP levels. It was shown to inhibit phenylephrine-stimulated contractions in rabbit aortic preparations with an IC₅₀ of 0.66 μM. Potentially useful for the treatment of cardiovascular disorders, hypertonia, thromboembolic disorders, ischemia, sexual dysfunction, inflammation and CNS disorders. Another exemplified compound is:



322251: C22 H17 F N8

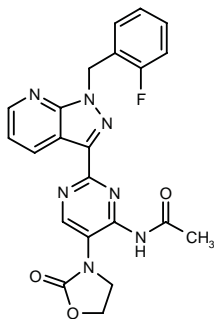
SOURCE – Bayer.

REFERENCES

1. Stasch, J.-P. et al. (Bayer AG) *Novel pyridine-substd. pyrazolopyridine derivs*. WO 0242301.

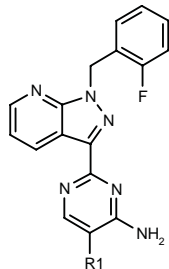
322252

N-[2-[1-(2-Fluorobenzyl)-1 H-pyrazolo[3,4-b]pyridin-3-yl]-5-(2-oxooxazolidin-3-yl)pyrimidin-4-yl]acetamide



C22 H18 F N7 O3; Mol wt: 447.4282

ACTION – Antihypertensive agent that activates soluble guanylate cyclase (sGC) and thereby increases cGMP levels. It was shown to inhibit phenylephrine-stimulated contractions in rabbit aortic preparations with an IC₅₀ of 0.25 μM. Potentially useful for the treatment of cardiovascular disorders, hypertonia, thromboembolic disorders, ischemia, sexual dysfunction, inflammation and CNS disorders. Other exemplified compounds are:



Compound	R1	Formula
322253	2-oxo-1-pyrrolidinyl	C ₂₁ H ₁₈ FN ₇ O
322254	2-oxo-1-Pip	C ₂₂ H ₂₀ FN ₇ O
322255	2-oxo-perhydro-1-azepinyl	C ₂₃ H ₂₂ FN ₇ O
322256	3,3,4,4-(Me)4-2-oxo-1-pyrrolidinyl	C ₂₅ H ₂₆ FN ₇ O
322257	3,3,4-(Me)3-2,5-dioxo-1-pyrrolidinyl	C ₂₄ H ₂₂ FN ₇ O ₂
322258	5,5-(Me)2-2,4-dioxo-3-oxazolidinyl	C ₂₂ H ₁₈ FN ₇ O ₃
322259	2-oxo-3-oxazolidinyl	C ₂₀ H ₁₆ FN ₇ O ₂
322260	2-oxo-3-thiazolidinyl	C ₂₀ H ₁₆ FN ₇ OS
322261	1-Me-2,4-dioxo-3-azabicyclo[3.1.0]hexan-3-yl	C ₂₃ H ₁₈ FN ₇ O ₂
322262	1,3-dioxo-2-isoindolinyl	C ₂₅ H ₁₆ FN ₇ O ₂

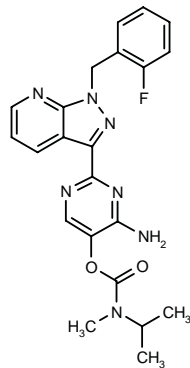
SOURCE – Bayer.

REFERENCES

1. Stasch, J.-P. et al. (Bayer AG) *Novel lactame-substd. pyrazolopyridine derivs.* WO 0242299.

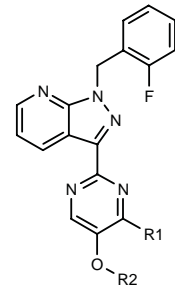
322263

N-Isopropyl-N-methylcarbamic acid 4-amino-2-[1-(2-fluorobenzyl)-1 H-pyrazolo[3,4-b]pyridin-3-yl]pyrimidin-5-yl ester



C22 H22 F N7 O2; Mol wt: 435.4608

ACTION – Antihypertensive agent that activates soluble guanylate cyclase (sGC) and thereby increases cGMP levels. It was shown to inhibit phenylephrine-stimulated contractions in rabbit aortic preparations with an IC₅₀ of 0.27 μM. Potentially useful for the treatment of cardiovascular disorders, hypertonia, thromboembolic disorders, ischemia, sexual dysfunction, inflammation and CNS disorders. Other exemplified compounds are:



Compound	R1	R2	Formula
322264	NH2	4-morpholinyl-CO	C ₂₂ H ₂₀ FN ₇ O ₃
322265	NH2	CON(allyl)2	C ₂₄ H ₂₂ FN ₇ O ₂
322266	Me	CON(CH2CO2Et)CH(Me)CH2OMe	C ₂₇ H ₂₉ FN ₆ O ₅
322267	NH2	CSN(Me)2	C ₂₀ H ₁₈ FN ₇ OS
322268	NHCON(Et)2	CON(Et)2	C ₂₇ H ₃₁ FN ₈ O ₃

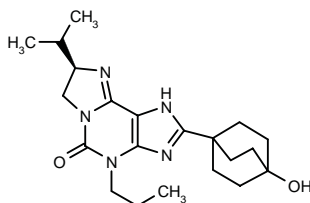
SOURCE – Bayer.

REFERENCES

1. Stach, J.-P. et al. (Bayer AG) *Novel carbamate-substd. pyrazolopyridine derivs.* DE 10057751, WO 0242300.

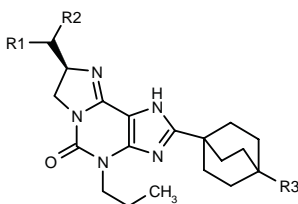
322350

2-(4-Hydroxybicyclo[2.2.2]oct-1-yl)-8(*R*)-isopropyl-4-propyl-4,5,7,8-tetrahydro-1*H*-imidazo[2,1-*f*]purin-5-one



C21 H31 N5 O2; Mol wt: 385.5089

ACTION – Potent and selective adenosine A₁ receptor antagonist that displayed a K_i of 4.4 nM at A₁ receptors in rat cerebral cortex preparations. Potentially useful for the treatment of hypertension, renal failure, diabetes, asthma, edema, congestive heart failure and renal dysfunction. Other specifically claimed condensed purine derivatives are:



Compound	R1	R2	R3	Formula
322351	H	Me	OH	C ₂₀ H ₂₉ N ₅ O ₂
322352	H	Me	CH ₂ CH ₂ CO ₂ H	C ₂₃ H ₃₃ N ₅ O ₃
322353	H	H	OH	C ₁₉ H ₂₇ N ₅ O ₂
322354	Me	Me	CH ₂ CH ₂ CO ₂ H	C ₂₄ H ₃₅ N ₅ O ₃

SOURCE – Biogen.

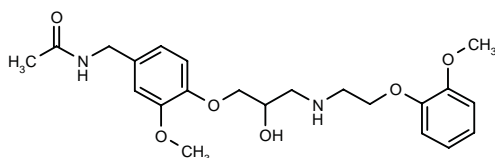
REFERENCES

1. Lin, K.-C. and Vu, C. (Biogen, Inc.) *Condensed purine derivs. as A₁ adenosine receptor antagonists*. WO 0244182.

KMUP-880602

321256

N-[4-[2-Hydroxy-3-[2-(2-methoxyphenoxy)ethyl-amino]propoxy]-3-methoxybenzyl]acetamide



C22 H30 N2 O6; Mol wt: 418.4870

ACTION – Dual α- and β-adrenoceptor blocker with selective β₁-adrenoceptor-blocking and vascular smooth muscle relaxation activities. It exhibited good affinity and selectivity for cardiac β₁-adrenoceptors (pK_i = 7.27) over lung β₂-adrenoceptors (pK_i = 6.08), and good affinity for brain α-adrenoceptors (pK_i = 8.25). *In vitro*, compound competitively antagonized isoproterenol-induced positive inotropic and chronotropic effects on atria (pA₂ = 7.24 and 7.42 in right and left atria, respectively) and tracheal relaxation responses (pA₂ = 6.24), as well as norepinephrine-induced contractions in isolated rat aorta with a pA₂ of 7.64. It also showed endothelium-independent and K⁺ channel opening-associated vasorelaxant activity. In anesthetized rats, compound dose-dependently (0.1-2.0 mg/kg i.v.) reduced mean blood pressure and heart rate, decreased isoproterenol-induced tachycardia in ganglion-blocked anesthetized rats (0.5-2.0 mg/kg i.v.), and inhibited the isoproterenol-induced tachycardia and phenylephrine-induced pressor response in reserpine-treated rats (0.5-2.0 mg/kg). Potentially useful for the treatment of hypertension.

SOURCE – Kaohsiung Medical College, Kaohsiung (TW).

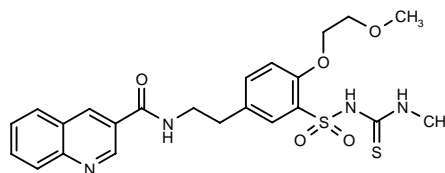
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1. Yeh, J.-L. et al. *Vanillylamide-based propanolamine derivative displays α/β-adrenoceptor blocking and vasodilating properties*. J Cardiovasc Pharmacol 2002, 39(6): 803.

TREATMENT OF DISORDERS OF THE CORONARY ARTERIES AND ATHEROSCLEROSIS

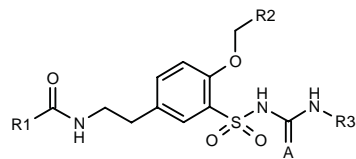
321373

N-[2-[4-(2-Methoxyethoxy)-3-(3-methylthioureido-sulfonyl)phenyl]ethyl]quinoline-3-carboxamide



C23 H26 N4 O5 S2; Mol wt: 502.6134

ACTION – An inhibitor of ATP-sensitive potassium channels in cardiac muscle cells and the vagal nervous system. Compound was able to prevent the hypoxia-induced shortening of APD₉₀ in pig papillary muscle by 42% at 2 μM. It is expected to display little hypoglycemic activity, since it is not able to block pancreatic ATP-sensitive potassium channel subunits SUR1 and Kir6.2 expressed in CHO cells. Potentially useful for the treatment of cardiac ischemia, coronary heart disease, weakened myocardial contractile force, cardiac insufficiency, cardiomyopathies and cardiac arrhythmia, as well as for preventing sudden cardiac death and improving cardiac function. Other exemplified benzenesulfonamide derivatives are:



Compound	R1	R2	R3	A	Formula
321374	3-quinolyl	CH2OCH2CF3	Me	S	C ₂₄ H ₂₅ F ₃ N ₄ O ₅ S ₂
321375	3-quinolyl	Et	Me	S	C ₂₃ H ₂₆ N ₄ O ₄ S ₂
321376	CH=C(Me)2	CH2OMe	Me	S	C ₁₈ H ₂₇ N ₃ O ₅ S ₂
321377	3-quinolyl	CH2OMe	Me	O	C ₂₃ H ₂₆ N ₄ O ₆ S
321378	3-quinolyl	CH2OPh	Me	S	C ₂₈ H ₂₈ N ₄ O ₅ S ₂
321379	1-cyclohexenyl	H	i-Pr	S	C ₂₀ H ₂₉ N ₃ O ₄ S ₂
321380	1-cyclohexenyl	H	cyclohexyl	S	C ₂₃ H ₃₃ N ₃ O ₄ S ₂

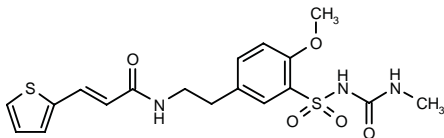
SOURCE – Aventis Pharma.

REFERENCES

1. Heitsch, H. and Englert, H.C. (Aventis Pharma Deutschland GmbH) *Acylaminoalkyl-substd. benzenesulfonamide derivs., their preparation, their use and pharmaceutical preparations comprising them.* DE 10054481, WO 0236556.

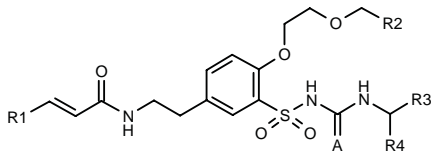
321381

N-[2-[4-Methoxy-3-(3-methylureidosulfonyl)phenyl]ethyl]-3-(2-thienyl)-2(E)-propenamide



C18 H21 N3 O5 S2; Mol wt: 423.5119

ACTION – An inhibitor of ATP-sensitive potassium channels in cardiac muscle cells and the vagal nervous system. Compound inhibited chloroform-induced ventricular fibrillation by 35% following a dose of 3 mg/kg i.p. to mice. In addition, it is expected to display little hypoglycemic activity, since it is not able to block pancreatic ATP-sensitive potassium channel subunits SUR1 and Kir6.2 expressed in CHO cells. Potentially useful for the treatment of cardiac ischemia, coronary heart disease, weakened myocardial contractile force, cardiac insufficiency, cardiomyopathies and cardiac arrhythmia, as well as for the prevention of sudden cardiac death and improving cardiac function. Other exemplified benzene-sulfonamide derivatives are:



Compound	R1	R2	R3	R4	A	Formula
321382	2-thienyl	H	H	H	O	C ₂₀ H ₂₅ N ₃ O ₆ S ₂
321383	2-thienyl	Me	H	H	S	C ₂₁ H ₂₇ N ₃ O ₅ S ₃
321384	2-Pyr	H	Me	Me	S	C ₂₃ H ₃₀ N ₄ O ₅ S ₂

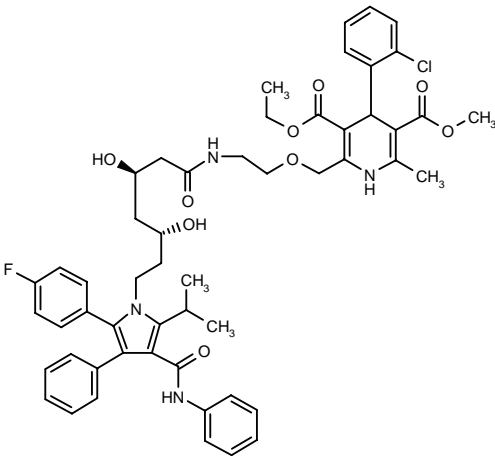
SOURCE – Aventis Pharma.

REFERENCES

1. Heitsch, H. and Englert, H.C. (Aventis Pharma Deutschland GmbH) *Heteroarylacryloylaminoalkyl-substd. benzenesulfonamide derivs., their preparation, their use and pharmaceutical preparations comprising them.* DE 10054482, WO 0236565.

321685

4-(2-Chlorophenyl)-2-[2-[7-[2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-(N-phenylcarbamoyl)-1H-pyrrol-1-yl]-3(R),5(R)-dihydroxyheptanamido]ethoxymethyl]-6-methyl-1,4-dihydropyridine-3,5-dicarboxylic acid 3-ethyl 5-methyl diester



C53 H58 Cl F N4 O9; Mol wt: 949.5112

ACTION – Mutual prodrug of the HMG-CoA reductase inhibitor atorvastatin and the calcium channel blocker amlodipine. The resulting compound, combining the lipid-lowering, antiischemic and antihypertensive properties of the parent drugs, is claimed for use in the treatment of atherosclerosis, angina pectoris, combined hypertension and hyperlipidemia, and for the management of cardiac risk.

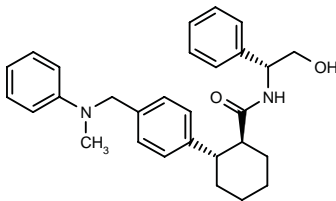
SOURCE – Pfizer.

REFERENCES

1. Crook, R.J. and Pettman, A.J. (Pfizer Ltd.;Pfizer Inc.) *Mutual prodrug of amlodipine and atorvastatin.* EP 1205477.

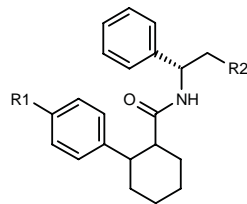
322143

(1S,2S)-N-[2-Hydroxy-1(R)-phenylethyl]-2-[4-(N-methyl-N-phenylaminomethyl)phenyl]cyclohexanecarboxamide

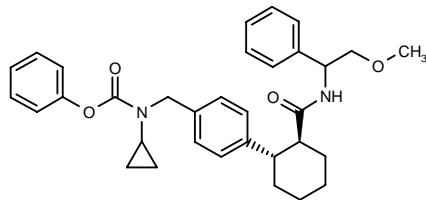


C29 H34 N2 O2; Mol wt: 442.5996

ACTION – Calcium-activated potassium (maxi-K) channel opener with activity in a rat model of cardiac ischemia. Potentially useful for the treatment of cardiovascular, cerebrovascular and urinary tract diseases. Other exemplified substituted cyclohexane derivatives are:



Compound	R1	R2	Isomer	Formula
322144	1-Pip-CON(Ph)CH2	OH	1S,2S	C ₃₄ H ₄₁ N ₃ O ₃
322145	1-pirrolidinyl-CON(Ph)CH2	H	1S,2S	C ₃₃ H ₃₈ N ₃ O ₂
322146	CH2N(cyclopropyl)CO2Ph	OH	1R,2R	C ₃₂ H ₃₈ N ₂ O ₄
322149	CH2N(CH2CH2OMe)CO2Ph	OH	1R,2R	C ₃₂ H ₃₈ N ₂ O ₅
322151	CH2N(Me)C(Me)2Ph	H	1S,2S	C ₃₂ H ₄₀ N ₂ O
322154	CON(Me)C(Me)2Ph	H	1S,2S	C ₃₂ H ₃₈ N ₂ O ₂
322155	CH2OPh	H	1S,2S	C ₂₈ H ₃₁ NO ₂



322153: C₃₃ H₃₈ N₂ O₄

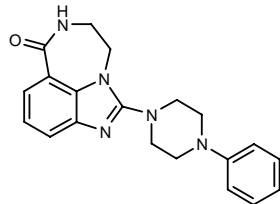
SOURCE – Bayer.

REFERENCES

1. Röhrig, S. et al. (Bayer AG) *Substd. cyclohexane derivatees and the use thereof in medicaments for treating cardiovascular diseases.* WO 0242257.

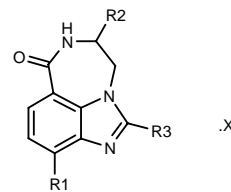
322182

2-(4-Phenylpiperazin-1-yl)-4,5,6,7-tetrahydroimidazo-[4,5,1-jk][1,4]benzodiazepin-7-one



C₂₀ H₂₁ N₅ O; Mol wt: 347.4199

ACTION – Poly(ADP-ribose)polymerase (PARP, NAD⁺ ADP-ribosyltransferase) inhibitor, potentially useful for the treatment of myocardial infarction, cardiac ischemia, cardiac insufficiency, atherosclerosis, postangioplasty restenosis, cerebral ischemia, cerebral infarction, neurodegenerative diseases, renal failure, inflammatory and immune disorders, rheumatic diseases, diabetes, pancreatitis, septic shock, acute respiratory distress syndrome, cancer, AIDS, hepatitis, psoriasis, ulcerative colitis, multiple sclerosis and myasthenia. Other exemplified benzimidazole derivatives are:



Compound	R1	R2	R3	X	Formula
322183	H	H	4-(4-Pyr)-1-Piz		C ₁₉ H ₂₀ N ₆ O
322184	H	H	4-(1-Pip)-1-Pip		C ₂₀ H ₂₇ N ₅ O
322185	H	H	4-(5-Me-4-imidazolyl)-1-Pip		C ₁₉ H ₂₂ N ₆ O
322186	H	Me	4-Ph-1-Piz		C ₂₁ H ₂₃ N ₅ O
322187	H	H	4-(t-BuOCO)-1-Piz		C ₁₉ H ₂₅ N ₅ O ₃
322188	H	H	1-Piz	2HCl	C ₁₄ H ₁₇ N ₅ O.2HCl
322189	H	Me	4-(t-BuOCO)-1-Piz		C ₂₀ H ₂₇ N ₅ O ₃
322190	H	Me	1-Piz	2HCl	C ₁₅ H ₁₉ N ₅ O.2HCl
322191	H	H	4-Ph-4-(t-BuOCONH)-1-Pip	2HCl	C ₂₆ H ₃₁ N ₅ O ₃ .2HCl
322192	H	H	4-NH2-4-Ph-1-Pip	2HCl	C ₂₁ H ₂₃ N ₅ O.2HCl
322193	Me	H	4-(cyclohexyl)-1-Piz		C ₂₁ H ₂₉ N ₅ O

SOURCE – Sanofi-Synthélabo.

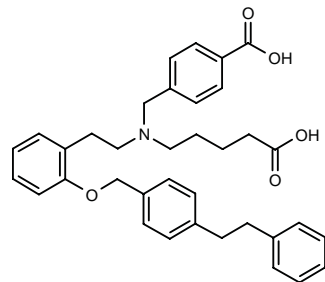
REFERENCES

1. Barth, F. et al. (Sanofi-Synthélabo) *Benzimidazole derivs., preparation and therapeutic use thereof.* WO 0242306.

BAY-58-2667*

302877

4-[N-(4-Carboxybutyl)-N-[2-[2-[4-(2-phenylethyl)benzyl-oxy]phenyl]ethyl]aminomethyl]benzoic acid



C₃₆ H₃₉ N O₅; Mol wt: 565.7061

ACTION – Soluble guanylyl cyclase (sGC) activator able to activate the enzyme in a nitric oxide (NO)- and heme-independent manner at concentrations as low as 1 nM. It exhibited potent vasorelaxant activity, as demonstrated by inhibition of phenylephrine-induced contractions in saphenous artery rings from normal and nitrate-tolerant rabbits (IC₅₀ = 0.16 and 0.22 nM, respectively); for comparison, glyceryl trinitrate was significantly less potent and less effective in tolerant vessels (IC₅₀ = 0.3 and 2.8 μM, respectively). Compound also concentration-dependently reduced coronary perfusion pressure in rat hearts and exhibited antiplatelet effects against U-46619-, collagen- and ADP-induced human platelet aggregation (IC₅₀ = 0.046, 1.1 and 7.5 μM, respectively). *In vivo* in a rat model of FeCl₃-induced arterial thrombosis, compound dose-dependently inhibited carotid artery thrombus formation with an ED₅₀ of 0.9 mg/kg p.o. In anesthetized dogs, both compound and glyceryl trinitrate significantly

decreased mean arterial blood pressure; although the two compounds exerted similar hemodynamic effects, the duration of action of Bay-58-2667 was much longer. Moreover, in conscious spontaneously hypertensive rats, doses of 3 and 10 mg/kg p.o. produced potent and long-lasting antihypertensive effects. Potentially useful for the treatment of cardiovascular diseases including angina, myocardial infarction and arterial thrombosis.

SOURCE – Bayer.

REFERENCES

1. Alonso-Alija, C. et al. (Bayer AG) *Novel derivs. of dicarboxylic acid having pharmaceutical properties*. DE 19943635, WO 0119780.

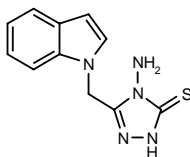
2. Stasch, J.-P. et al. *NO- and haem-independent activation of soluble guanylyl cyclase: Molecular basis and cardiovascular implications of a new pharmacological principle*. Br J Pharmacol 2002, 136(5): 773.

*Identified compound **302877** (see **302875**) Drug Data Rep 2001, 023(08): 0765.

C-6458*

315635

4-Amino-5-(1*H*-indol-1-ylmethyl)-3,4-dihydro-2*H*-1,2,4-triazole-3-thione



C11 H11 N5 S; Mol wt: 245.3089

ACTION – Indole derivative with significant antioxidant and free radical-scavenging activity *in vitro* in a rat hepatic microsomal lipid peroxidation assay. It was also active against the oxidative damage of the myocardium after ischemia–reperfusion injury in rabbits, where i.v. infusion of doses of 100 and 200 μ M during ischemia and reperfusion significantly reduced malondialdehyde levels in the myocardium; the higher dose significantly decreased infarct size in these animals. Potentially useful for the treatment of myocardial infarction.

SOURCES – Aristotle University of Thessaloniki, Thessaloniki (GR); University of Athens, Athens (GR); Onassis Cardiac Surgery Center, Athens (GR).

REFERENCES

1. Andreadou, I. et al. *Antioxidant activity of novel indole derivatives and protection of the myocardial damage in rabbits*. Chem Pharm Bull 2002, 50(2): 165.

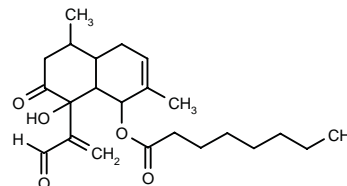
2. Andreadou, I. et al. *Cardioprotective effects of a novel indole derivative with antioxidant properties against ischemic reperfusion injury*. J Mol Cell Cardiol 2002, 34(6): A5.

*Identified compound **315635** Drug Data Rep 2002, 024(03): 0231.

F-16053A

321163

Octanoic acid 8-(1-formylvinyl)-8-hydroxy-2,5-dimethyl-7-oxo-1,4,4a,5,6,7,8,8a-octahydronaphthalen-1-yl ester



C23 H34 O5; Mol wt: 390.5166

ACTION – Sphingosine kinase inhibitor isolated from cultures of *Stereum ochraceoflavum* SANK 19400 (FERM BP-7244). F-16053A was shown to inhibit sphingosine kinase isozymes 1 and 2 with IC₅₀ values of 5.1 and 10.9 μ g/ml, respectively. Potentially useful for the treatment of arteriosclerosis, diabetes, thrombosis, inflammatory and autoimmune diseases, cancer and restenosis following PTCA.

SOURCE – Sankyo.

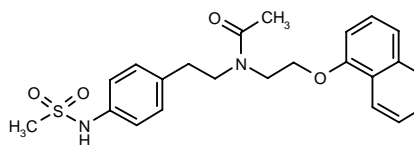
REFERENCES

1. Kohno, K. et al. (Sankyo Co., Ltd.) *Novel cpd. F-16053A*. JP 2002114741.

ANTIARRHYTHMIC DRUGS

321502

N-[2-[4-(Methylsulfonamido)phenyl]ethyl]-*N*-[2-(naphthalen-1-yloxy)ethyl]acetamide



C23 H26 N2 O4 S; Mol wt: 426.5344

ACTION – Class III antiarrhythmic, a dofetilide analogue with improved activity in prolonging effective refractory period (ERP; 58 and 24%, respectively at 10 μ M) and in reducing heart rate and cardiac muscle constriction in guinea pig spontaneously beating atria.

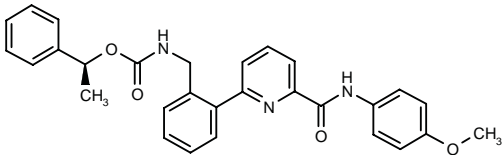
SOURCES – China Pharmaceutical University, Nanjing (CN); Chinese Academy of Sciences, Beijing (CN).

REFERENCES

1. Liu, H. et al. *New p-methylsulfonamido phenylamine analogues as class III antiarrhythmic agents: Design, synthesis, biological assay, and 3D-QSAR analysis*. J Med Chem 2002, 45(14): 2953.

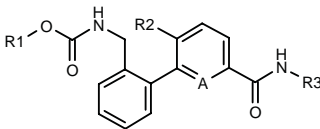
322366

N-[2-[6-[N-(4-Methoxyphenyl)carbamoyl]pyridin-2-yl]benzyl]carbamic acid 1(S)-phenylethyl ester

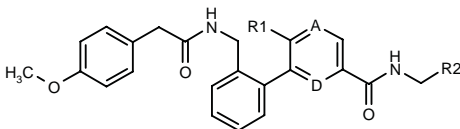


C29 H27 N3 O4; Mol wt: 481.5493

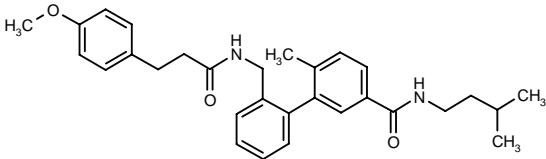
ACTION – Potassium channel blocker that inhibited human Kv1.5 channels expressed in *Xenopus* oocytes with an IC₅₀ of 2 μM. Potentially useful for the treatment of atrial arrhythmias. Other exemplified bis-aryl compounds are:



Compound	R1	R2	R3	A	Formula
322367	t-Bu	H	i-BuCH2	CH	C ₂₄ H ₃₂ N ₂ O ₃
322368	t-Bu	Me	i-BuCH2	CH	C ₂₅ H ₃₄ N ₂ O ₃
322369	t-Bu	H	i-BuCH2	N	C ₂₃ H ₃₁ N ₃ O ₃
322370	t-Bu	H	4-MeO-Ph	N	C ₂₅ H ₂₇ N ₃ O ₄
322371	(S)-CH(Me)Ph	H	2-Pyr-CH2CH2	N	C ₂₉ H ₂₈ N ₄ O ₃
322372	CH2Ph	Me	i-BuCH2	CH	C ₂₈ H ₃₂ N ₂ O ₃
322373	(S)-CH(Me)Ph	H	(S)-CH(i-Bu)CONH2	N	C ₂₈ H ₃₂ N ₄ O ₄



Compound	R1	R2	A	D	Formula
322374	H	2,4-(F)2-Ph	CH	N	C ₂₉ H ₂₅ F ₂ N ₃ O ₃
322375	H	2,4-(F)2-Ph	N	CH	C ₂₉ H ₂₅ F ₂ N ₃ O ₃
322376	H	2,4-(F)2-Ph	CH	CH	C ₃₀ H ₂₆ F ₂ N ₂ O ₃
322377	H	i-Bu	CH	CH	C ₂₈ H ₃₂ N ₂ O ₃
322378	Me	i-Bu	CH	CH	C ₂₉ H ₃₄ N ₂ O ₃



322379: C30 H36 N2 O3

SOURCE – Aventis Pharma.

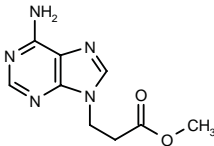
REFERENCES

1. Peukert, S. et al. (Aventis Pharma Deutschland GmbH) *Ortho-substd. and meta-substd. bis-aryl cpds., method for the production thereof, their use as a medicament, and pharmaceutical preparations containing these cpds.*. DE 10059418, WO 0244137.

HEART FAILURE THERAPY

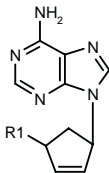
321821

3-(Adenin-9-yl)propionic acid methyl ester

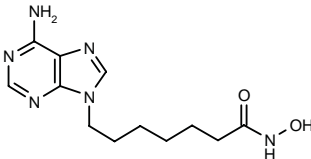


C9 H11 N5 O2; Mol wt: 221.2189

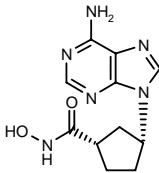
ACTION – Adenylyl cyclase inhibitor with potential in the treatment of congestive heart failure. Other exemplified adenine derivatives include the following:



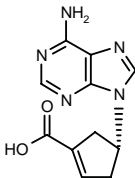
Compound	R1	Isomer	Formula
321823	OCH2CO2H	1R,4S	C ₁₂ H ₁₃ N ₅ O ₃
321824	CH2CO2H	1R,4R	C ₁₂ H ₁₃ N ₅ O ₂
321826	CONHOH	1S,4S	C ₁₁ H ₁₂ N ₆ O ₂
321827	CONHOH	1R,4R	C ₁₁ H ₁₂ N ₆ O ₂
321828	CO2H	1R,4S	C ₁₁ H ₁₁ N ₅ O ₂
321829	CO2H	1S,4S	C ₁₁ H ₁₁ N ₅ O ₂



321822: C12 H18 N6 O2



321825: C11 H14 N6 O2



321830: C11 H11 N5 O2

SOURCE – Millennium.

REFERENCES

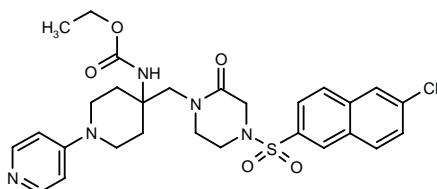
1. Levy, D.E. et al. (COR Therapeutics, Inc.) *Adenine based inhibitors of adenylyl cyclase, pharmaceutical compsns. and method of use thereof.* WO 0240481.

AGENTS AFFECTING BLOOD COAGULATION

ANTICOAGULANTS

321358

N-[4-[4-(6-Chloronaphthalen-2-ylsulfonyl)-2-oxopiperazin-1-ylmethyl]-1-(4-pyridyl)piperidin-4-yl]carbamic acid ethyl ester



C₂₈ H₃₂ Cl N₅ O₅ S; Mol wt: 586.1098

ACTION – Carbamate derivative with factor Xa-inhibitory activity (IC_{50} = 0.0046 μ M), giving a CT2 value (concentration required to double coagulation time) of 0.27 μ M in human plasma treated with rabbit brain-derived tissue thromboplastin. Potentially useful as an anticoagulant in the treatment of myocardial infarction, cerebral thrombosis, deep venous thrombosis, pulmonary thromboembolism, inflammation, cancer, cardiogenic thrombosis such as atrial fibrillation and cerebral infarction associated with atherosclerotic lesions.

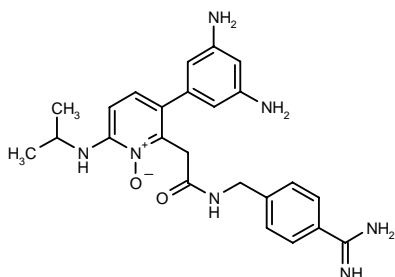
SOURCE – Takeda.

REFERENCES

1. Itoh, F. et al. (Takeda Chemical Industries, Ltd.) *Carbamate derivs., process for producing the same and use thereof*. WO 0238560.

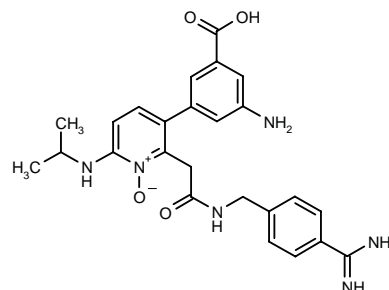
322036

N-(4-Amidinobenzyl)-2-[3-(3,5-diaminophenyl)-6-(isopropylamino)-1-oxidopyridin-2-yl]acetamide



C₂₄ H₂₉ N₇ O₂; Mol wt: 447.5401

ACTION – Agent with the ability to inhibit serine proteases of the coagulation cascade, giving IC_{50} values of 0.084, > 100, 60.7 and 0.022 μ M, respectively, against factor VIIa, factor Xa, thrombin and trypsin. Potentially useful for the treatment of thrombotic conditions such as venous and pulmonary embolism, deep venous thrombosis, cardiogenic thromboembolism, thromboembolic stroke, thrombosis associated with cancer and cancer chemotherapy, and unstable angina. Another exemplified compound is:



322037: C₂₅ H₂₈ N₆ O₄

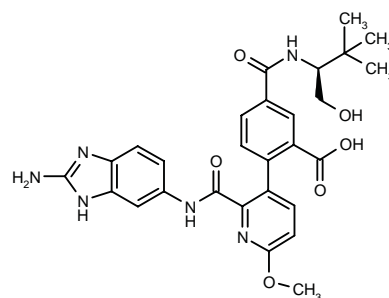
SOURCE – Pharmacia.

REFERENCES

1. South, M.S. et al. (Pharmacia Corp.) *Substd. polycyclic aryl and heteroaryl pyridines useful for selective inhibition of the coagulation cascade*. WO 0242272.

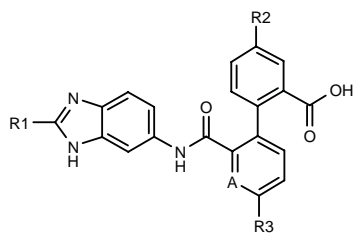
322167

2-[2-[*N*-(2-Amino-1*H*-benzimidazol-6-yl)carbamoyl]-6-methoxypyridin-3-yl]-5-[*N*-[1(*S*)-(hydroxymethyl)-2,2-dimethylpropyl]carbamoyl]benzoic acid

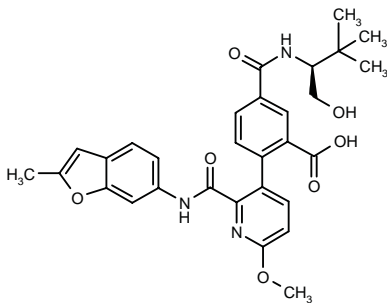


C₂₈ H₃₀ N₆ O₆; Mol wt: 546.5810

ACTION – Inhibitor of serine proteases such as factor VIIa, factor IXa, factor Xa, factor XIa, trypsin and urokinase. Potentially useful as an anticoagulant in the treatment of cardiovascular disorders, as well as for immune and inflammatory disorders and cancer. Other exemplified compounds include the following:



Compound	R1	R2	R3	A	Formula
322168	H	(S)-CONHCH(t-Bu)CH2OH	H	CH	C ₂₈ H ₂₈ N ₄ O ₅
322170	NH2	CONHCH(i-Pr)2	OMe	N	C ₂₉ H ₃₂ N ₆ O ₅
322171	NH2	2,4-(Cl)2-PhCH2CH2NHCO	OMe	N	C ₃₀ H ₂₄ Cl ₂ N ₆ O ₅
322172	NH2	CONHCH2CH2OPh	OMe	N	C ₃₀ H ₂₆ N ₆ O ₆
322173	NH2	2,5-(MeO)2-PhCH2CH2NHCO	OMe	N	C ₃₂ H ₃₀ N ₆ O ₇
322174	NH2	OMe	OMe	N	C ₂₂ H ₁₉ N ₅ O ₅
322175	NH2	t-BuCH2NHCO	OEt	N	C ₂₈ H ₃₀ N ₆ O ₅



322169: C30 H31 N3 O7

SOURCE – Bristol-Myers Squibb.

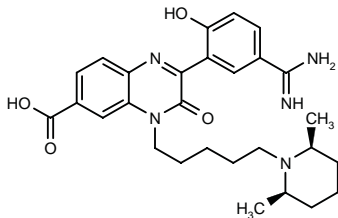
REFERENCES

1. Bisacchi, G.S. et al. (Bristol-Myers Squibb Co.) *Acid derivs. useful as serine protease inhibitors*. WO 0242273.

PD-313052

321988

cis-2-(5-Amidino-2-hydroxyphenyl)-4-[5-(2,6-dimethyl-piperidin-1-yl)pentyl]-3-oxo-3,4-dihydroquinoxaline-6-carboxylic acid



C28 H35 N5 O4; Mol wt: 505.6155

ACTION – Anticoagulant, a potent, selective and direct inhibitor of factor Xa ($K_i = 0.5$ nM) active *in vivo* in a canine model of electrolytic injury-induced arterial and venous thrombosis. When compound was given as a continuous infusion (0.625, 1.25 and 2.5 mg/kg/min) from 90 min before injury to 4 h after injury, a prolongation of the time to formation of an occlusive thrombus in both arteries and veins was seen (133-199 min for compound and 87 min for control); thrombus mass in arteries and veins was also reduced. No significant difference in blood loss from surgical sites and less than a 2-fold increase in template bleeding time were seen in comparison with the control group.

SOURCE – Pfizer.

REFERENCES

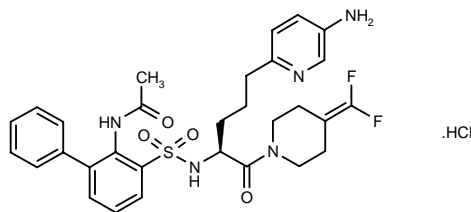
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2. McClanahan, T.B. et al. *The antithrombotic effects of PD 313052, a potent and selective inhibitor of Xa, in a canine electrolytic injury model of venous and arterial thrombosis*. Pharmacologist 2002, 44(2, Suppl. 1): Abst 21.5.

SSR-182289

305816

N-[3-[*N*-[4-(5-Aminopyridin-2-yl)-1(*S*)-[4-(difluoromethylene)piperidin-1-ylcarbonyl]butyl]sulfamoyl]-biphenyl-2-yl]acetamide hydrochloride



C30 H33 F2 N5 O4 S . HCl; Mol wt: 634.1446

ACTION – Potent, orally active thrombin inhibitor ($K_i = 31$ nM against human thrombin) with good selectivity over other proteases including trypsin ($K_i = 54$ μ M), factor Xa ($K_i = 167$ μ M), factor VIIa, factor IXa, plasmin, urokinase, tPA, kallikrein and APC ($K_i > 250$ μ M). It showed potent anticoagulant activity in human plasma, with respective EC_{100} values of 96 and 805 nM for doubling thrombin time and activated partial thromboplastin time. It inhibited thrombin-induced aggregation of human platelet ($IC_{50} = 32$ nM) but was inactive against other platelet agonists ($IC_{50} > 10$ μ M). *Ex vivo* in conscious dogs, compound displayed potent anticoagulant effects after both i.v. (0.1-1 mg/kg) and oral doses (3 and 5 mg/kg); after oral doses, the effect of compound lasted up to 8 h. Oral antithrombotic efficacy was also seen in a rat venous thrombosis model ($ED_{50} = 1.1$ mg/kg p.o.).

SOURCE – Sanofi-Synthélabo.

REFERENCES

1. Altenburger, J.-M. et al. (Sanofi-Synthélabo) *N-(Heterocyclyl)benzene or pyridine sulphonamides as antithrombotic agents and anticoagulants*. WO 0170736.

2. O'Connor, S.E. et al. *SSR182289, a novel orally-active thrombin inhibitor*. Pharmacologist 2002, 44(2, Suppl. 1): Abst 21.1.

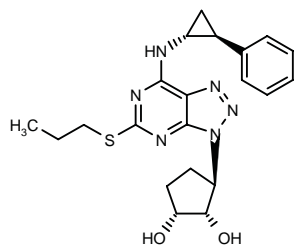
3. *R&D portfolio*. Sanofi-Synthelabo Web Site 2001, Aug 31.

4. *R&D portfolio*. Sanofi-Synthelabo Web Site 2002, March 1.

ANTIPLATELET THERAPY

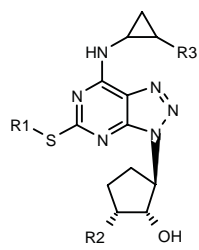
321086

3(*R*)-[7-[(1*R**,2*S**)-2-Phenylcyclopropylamino]-5-(propylsulfanyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]cyclopentane-1(*R*),2(*S*)-diol



C21 H26 N6 O2 S; Mol wt: 426.5424

ACTION – Antithrombotic agent that acts as an antagonist at P_{2T} (also known as P2Y_{ADP} or P2Y₁₂) receptors. Potentially useful for the treatment of myocardial infarction, thrombotic stroke, transient ischemic attacks, peripheral vascular disease and unstable or stable angina. Other specifically claimed compounds are:



Compound	R1	R2	R3	Isomer	Formula
321087	Pr	OH	4-Me-Ph	trans	C ₂₂ H ₂₈ N ₆ O ₂ S
321088	Me	OH	Ph	trans	C ₁₉ H ₂₂ N ₆ O ₂ S
321089	Pr	OH	H		C ₁₅ H ₂₂ N ₆ O ₂ S
321090	4-CF3-Ph	OH	H		C ₁₉ H ₁₉ F ₃ N ₆ O ₂ S
321091	Bu	OH	Ph	trans	C ₂₂ H ₂₈ N ₆ O ₂ S
321092	Bu	OH	4-Cl-Ph	trans	C ₂₂ H ₂₇ ClN ₆ O ₂ S
321093	Pr	H	Ph	trans	C ₂₁ H ₂₈ N ₆ OS
321094	Pr	H	3,4-(F)2-Ph	trans	C ₂₁ H ₂₄ F ₂ N ₆ OS

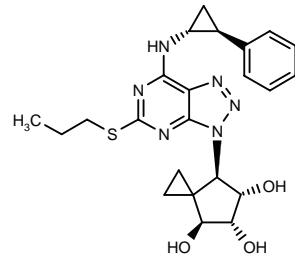
SOURCE – AstraZeneca.

REFERENCES

1. Brown, R. et al. (AstraZeneca AB) *Novel cpds.* WO 0238570.

321096

7(*R*)-[7-[(1*R*,2*S*)-2-Phenylcyclopropylamino]-5-(propylsulfanyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]spiro[2.4]heptane-4(*S*),5(*R*),6(*S*)-triol



C23 H28 N6 O3 S; Mol wt: 468.5792

ACTION – Antithrombotic agent that acts as an antagonist at P_{2T} (also known as P2Y_{ADP} or P2Y₁₂) receptors. Potentially useful for the treatment of myocardial infarction, thrombotic stroke, transient ischemic attacks, peripheral vascular disease and unstable or stable angina.

SOURCE – AstraZeneca.

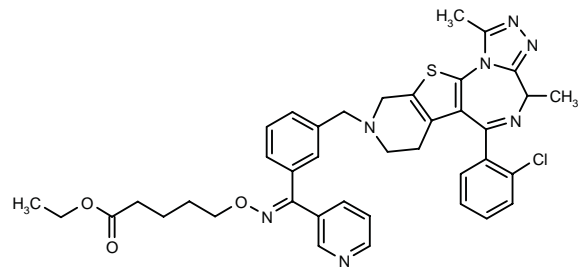
REFERENCES

1. Guile, S. and Martin, B. (AstraZeneca AB) *Novel cpds.* WO 0238571.

GK-04489

316971

5-[1-[3-[6-(2-Chlorophenyl)-1,4-methyl-7,8,9,10-tetrahydro-4*H*-pyrido[4',3':4,5]thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-9-ylmethyl]phenyl]-1-(3-pyridyl)-methylideneaminoxy]pentanoic acid ethyl ester



C39 H40 Cl N7 O3 S; Mol wt: 722.3100

ACTION – Dual TxA₂ synthetase inhibitor and PAF antagonist able to prolong the time to occlusion in a rat model of photochemically induced arterial thrombosis. In a model of cerebral ischemia in rats induced by bilateral carotid artery ligation, compound prolonged survival time and reduced infarct size by preserving regional blood flow. For comparison, the TxA₂ synthetase inhibitor ozagrel and the PAF antagonist UK-74505 were inactive in this model. Potentially useful for the treatment of ischemic stroke and thrombosis.

SOURCE – Nikken Chemicals.

REFERENCES

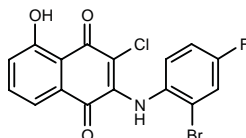
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2. Kaneko, Y. et al. *Effect of a novel agent combining TxA₂ synthetase inhibitor with PAF antagonist, GK-04489, on cerebral ischemia in the rat carotid ligation model.* Jpn J Pharmacol 2002, 88(Suppl. 1): Abst P-61.

J-78

321943

2-(2-Bromo-4-fluorophenylamino)-3-chloro-5-hydroxy-1,4-naphthoquinone



C16 H8 Br Cl F N O3; Mol wt: 396.5982

ACTION – Antithrombotic agent able to inhibit collagen-, thrombin- and A23187-induced human platelet aggregation *in vitro* without effects on coagulation parameters in human plasma. Dose-dependent *ex vivo* inhibition of ADP- and collagen-induced rat platelet aggregation was also seen, and in a murine pulmonary thrombosis model, compound was found to dose-dependently protect mice from death.

SOURCES – Chungbuk National University, Chungbuk (KR); Ewha Womans University, Seoul (KR); Konkuk University, Chungbuk (KR).

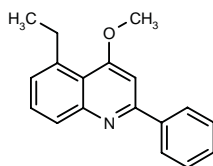
REFERENCES

1. Jin, Y.-R. et al. *Antithrombotic activity of J78, a newly synthesized 1,4-naphthoquinone derivative*. Pharmacologist 2002, 44(2, Suppl. 1): Abst 21.3.

KTC-5

299778

5-Ethyl-4-methoxy-2-phenylquinoline



C18 H17 N O; Mol wt: 263.3383

ACTION – Antiplatelet agent able to selectively inhibit arachidonic acid- and collagen-induced human platelet aggregation (IC_{50} = 0.11 and 0.20 μ M, respectively) and ATP release, but having no effect against thrombin or U-46619. It also inhibited arachidonic acid-induced TxB_2 formation (IC_{50} = 0.07 μ M) and inhibited lipopolysaccharide-induced PGE_2 formation in the presence of arachidonic acid (IC_{50} = 0.17 μ M) in RAW264.7 cells. The involvement of cyclooxygenase inhibition in the compound's mechanism of action was suggested.

SOURCES – Chang Gung University, Taoyuan (TW); China Medical College, Taichung (TW); National Taiwan University, Taipei (TW).

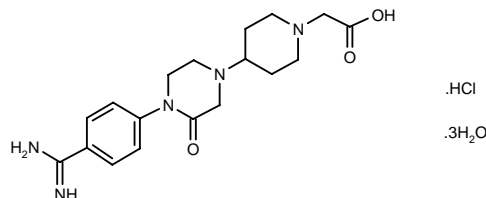
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YM-57029*

241633

2-[4-[4-(4-Amidinophenyl)-3-oxopiperazin-1-yl]piperidin-1-yl]acetic acid monohydrochloride trihydrate



C18 H25 N5 O3 . HCl . 3H2O; Mol wt: 449.9328

ACTION – Oral antithrombotic agent, the active metabolite of the double prodrug YM-128** a $gPIIb/IIIa$ receptor antagonist with an IC_{50} value of 14 nM for inhibition of biotinylated fibrinogen binding to $gPIIb/IIIa$, and IC_{50} values of 0.023 and 0.025 μ M for inhibition of ADP- and collagen-induced aggregation of human platelet-rich plasma, respectively. It was also active against high shear stress-induced human platelet aggregation (IC_{50} = 17 nM) as well as ADP-induced ATP release from human platelets (IC_{50} = 8.4 nM). It was able to enhance platelet deaggregation following ADP-induced aggregation (EC_{50} = 350 nM) and showed little proaggregatory activity. *Ex vivo* studies in guinea pigs showed that compound dose-dependently inhibited ADP-induced platelet aggregation, giving almost complete inhibition of platelet aggregation following an i.v. bolus of 30 μ g/kg; it also inhibited platelet retention to collagen beads (84% inhibition). *In vivo*, compound dose-dependently inhibited thrombus formation in a carotid artery thrombosis model and the arteriovenous shunt model in guinea pigs at doses of 10 and 30 mg/kg i.v., respectively; this effect was associated with prolongation of the bleeding time.

SOURCE – Yamanouchi.

REFERENCES

1. Akamatsu, S. et al. (Yamanouchi Pharmaceutical Co., Ltd.) *Novel benzamidine derivs. and medicinal compsn. thereof*. EP 0810215, JP 1996333341, JP 1996333342, US 5773442, WO 9624583.
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4. Moritani, Y. et al. *Pharmacological properties of YM-57029, a novel platelet glycoprotein IIb/IIIa antagonist*. Eur J Pharmacol 2002, 439(1-3): 43.
5. Suzuki, K.-I. et al. *Pharmacodynamics and pharmacokinetics of YM128 a GPIIb/IIIa antagonist*. Drug Dev Res 2002, 55(3): 149.

*Identified compound **241633** (see **240957**) Drug Data Rep 1997, 019(01): 0047.

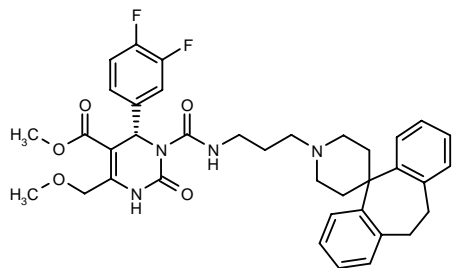
See **YM-68128 Drug Data Rep 2000, 022(02): 0150.

RENAL–UROLOGIC DRUGS

BENIGN PROSTATIC HYPERPLASIA THERAPY

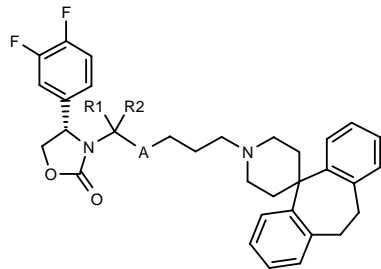
321183

6(S)-(3,4-Difluorophenyl)-1-[N-[3-(10,11-dihydro-5H-spiro[dibenzo[a,d]cycloheptene-5,4'-piperidin]-1'-yl)-propyl]carbamoyl]-4-(methoxymethyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester



C37 H40 F2 N4 O5; Mol wt: 658.7420

ACTION – α_{1A} -Adrenoceptor antagonist for use in the treatment of benign prostatic hyperplasia. Other specifically claimed tricyclic spiro compounds are:



Compound	R1	R2	A	Formula
321184		-O-	NH	C ₃₂ H ₃₃ F ₂ N ₃ O ₃
321186	H	H	CH2	C ₃₃ H ₃₆ F ₂ N ₂ O ₂

SOURCE – Merck & Co.

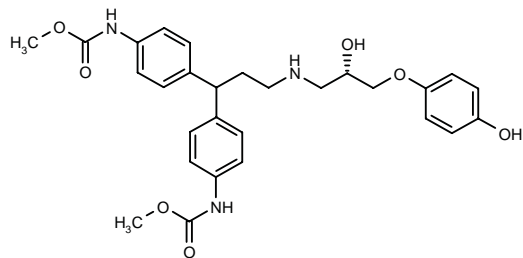
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1. Evans, B.E. et al. (Merck & Co., Inc.) *Spirotricyclic substd. azacycloalkane derivs. and uses thereof*. US 6387893.

TREATMENT OF URINARY INCONTINENCE

321324

N,N'-[3-[2(S)-Hydroxy-3-(4-hydroxyphenoxy)propyl-amino]propylidene]bis(1,4-phenylene)bis(carbamic acid methyl ester)



C28 H33 N3 O7; Mol wt: 523.5827

ACTION – β_3 -Adrenoceptor agonist, potentially useful for the treatment of pollakiuria, urinary incontinence, obesity and diabetes. It reduced the carbachol-induced increase in intravesical pressure by 30% following administration to anesthetized dogs at a dose of 1.8 μ g/kg i.v.

SOURCE – Fujisawa.

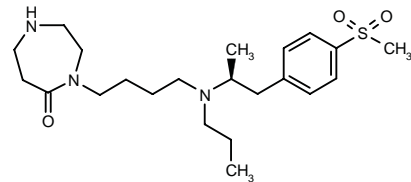
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RO-3202904

322000

4-[4-[N-[1(S)-Methyl-2-[4-(methylsulfonyl)phenyl]ethyl]-N-propylamino]butyl]perhydrodiazepin-5-one



C22 H37 N3 O3 S; Mol wt: 423.6183

ACTION – Competitive bladder-selective muscarinic receptor antagonist ($pK_i = 7.2, 7.9, 7.5, 7.7$ and 5.8 at M_1, M_2, M_3, M_4 and M_5 receptors, respectively). In anesthetized rats, compound dose-dependently inhibited saline-induced rhythmic bladder contractions ($ED_{50} = 0.04$ mg/kg i.v.) with an efficacy comparable to that of tolterodine ($ED_{50} = 0.08$ mg/kg i.v.). In a model of pilocarpine-induced salivation, compound was less active than tolterodine ($ED_{50} = 2.25$ and 0.19 mg/kg i.v.) and gave a bladder/salivation selectivity ratio of $1:56.3$ versus $1:9.5$ for tolterodine. Similar results were obtained in anesthetized dogs where the ED_{50} values for inhibition of parasympathetic nerve stimulation-induced bladder contractions were 0.006 and 0.08 mg/kg i.v. for compound and tolterodine, respectively. In this assay, the respective bladder/salivation selectivity ratios were $1:8.5$ and $1:2.2$. In a model of pilocarpine-induced bladder contraction in conscious dogs, compound and tolterodine (0.1 - 1 mg/kg) produced a dose-dependent inhibition of bladder contraction but compound at a dose of 0.3 mg/kg had significant bladder selectivity compared to the tolterodine. Significant increase in heart rate was seen with a dose of 3 mg/kg of compound and 1 mg/kg of tolterodine; no behavioral effects were seen with compound at pharmacological doses. Potentially useful for the treatment of overactive bladder.

SOURCES – Advanced Medicine; Roche Bioscience; Tularik.

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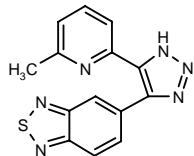
2. Greene, B. et al. *The effect of the muscarinic antagonists RO3202904 (RO), tolterodine (TOL) and oxybutynin (OXY) on pilocarpine (PIL)-induced bladder contraction and salivation in conscious dogs*. Pharmacologist 2002, 44(2, Suppl. 1): Abst 25.12.

3. Shetty, S.G. et al. *RO3202904: A novel urinary bladder selective antimuscarinic*. Pharmacologist 2002, 44(2, Suppl. 1): Abst 25.7.

TREATMENT OF RENAL DISEASES

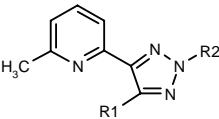
321841

5-[5-(6-Methylpyridin-2-yl)-1*H*-1,2,3-triazol-4-yl]-2,1,3-benzothiadiazole

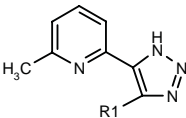


C14 H10 N6 S; Mol wt: 294.3410

ACTION – An inhibitor of the transforming growth factor- β (TGF- β) signaling pathway that acts by inhibiting the phosphorylation of smad2 and smad3 by ALK5 kinase. Potentially useful for the treatment of chronic and acute renal diseases, wound healing, arthritis, osteoporosis, congestive heart failure, ulcers, ocular disorders, diabetic nephropathy, impaired neurological function, Alzheimer's disease, atherosclerosis, fibrotic disorders and restenosis. Other specifically claimed compounds are:



Compound	R1	R2	Formula
321842	2,1,3-benzothiadiazol-5-yl	Et	C ₁₆ H ₁₄ N ₆ S
321845	1,4-benzodioxan-6-yl	H	C ₁₆ H ₁₄ N ₄ O ₂
321846	1-Me-6-benzimidazolyl	H	C ₁₆ H ₁₄ N ₆
321847	[1,2,4]triazolo[1,5-a]pyridin-6-yl	Et	C ₁₆ H ₁₅ N ₇
321848	[1,2,4]triazolo[1,5-a]pyridin-6-yl	Me	C ₁₅ H ₁₃ N ₇
321849	4-MeO-Ph	H	C ₁₅ H ₁₄ N ₄ O
321850	3-F-4-MeO-Ph	H	C ₁₅ H ₁₃ FN ₄ O
321851	3-Cl-4-MeO-Ph	H	C ₁₅ H ₁₃ ClN ₄ O



Compound	R1	Formula
321843	[1,2,4]triazolo[1,5-a]pyridin-6-yl	C ₁₄ H ₁₁ N ₇
321844	2,3-dihydro-5-benzofuryl	C ₁₆ H ₁₄ N ₄ O

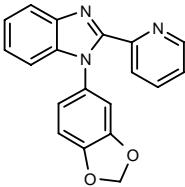
SOURCE – GlaxoSmithKline.

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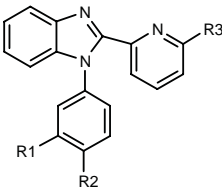
321996

1-(1,3-Benzodioxol-5-yl)-2-(2-pyridyl)-1*H*-benzimidazole



C19 H13 N3 O2; Mol wt: 315.3307

ACTION – An inhibitor of the transforming growth factor- β (TGF- β) signaling pathway that acts by inhibiting the phosphorylation of smad2 and smad3 by ALK5 kinase. Potentially useful for the treatment of chronic and acute renal diseases, wound healing, arthritis, osteoporosis, congestive heart failure, ulcers, ocular disorders, diabetic nephropathy, impaired neurological function, Alzheimer's disease, atherosclerosis, fibrotic disorders and restenosis. Other exemplified compounds are:



Compound	R1	R2	R3	Formula
321997	-OCH2O-		Me	C ₂₀ H ₁₅ N ₃ O ₂
321998	Cl	OMe	H	C ₁₉ H ₁₄ ClN ₃ O
322001	Cl	OMe	Me	C ₂₀ H ₁₆ ClN ₃ O

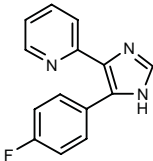
SOURCE – GlaxoSmithKline.

REFERENCES

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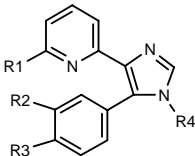
322004

2-[5-(4-Fluorophenyl)-1*H*-imidazol-4-yl]pyridine

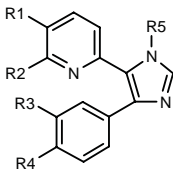


C14 H10 F N3; Mol wt: 239.2520

ACTION – An inhibitor of the transforming growth factor-β (TGF-β) signaling pathway that acts by inhibiting the phosphorylation of smad2 and smad3 by ALK5 kinase. Potentially useful for the treatment of chronic and acute renal diseases, wound healing, arthritis, osteoporosis, congestive heart failure, ulcers, ocular disorders, diabetic nephropathy, impaired neurological function, Alzheimer’s disease, atherosclerosis, fibrotic disorders and restenosis. Other exemplified compounds are:



Compound	R1	R2	R3	R4	Formula
322007	H	-OCH2O-	H	H	C ₁₅ H ₁₁ N ₃ O ₂
322008	Me	-OCH2O-	H	H	C ₁₆ H ₁₃ N ₃ O ₂
322009	Br	-OCH2O-	H	H	C ₁₅ H ₁₀ BrN ₃ O ₂
322011	Me	-OCH2CH2O-	H	H	C ₁₇ H ₁₅ N ₃ O ₂
322016	Me	-OCH2CH2O-	Me	H	C ₁₈ H ₁₇ N ₃ O ₂
322017	NHPh	-OCH2O-	H	H	C ₂₁ H ₁₆ N ₄ O ₂
322018	NHPh	H	F	H	C ₂₀ H ₁₅ FN ₄



Compound	R1	R2	R3	R4	R5	Formula
322014	-CH=CHCH=CH-	H	F	H	H	C ₁₈ H ₁₂ FN ₃
322015	H	Me	-OCH2CH2O-	Me	H	C ₁₈ H ₁₇ N ₃ O ₂

SOURCE – GlaxoSmithKline.

REFERENCES

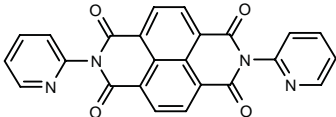
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GASTROINTESTINAL DRUGS

ANTIULCER DRUGS

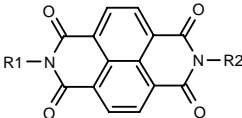
322156

2,7-Bis(2-pyridyl)benzo[*lmn*]-3,8-phenanthroline-1,3,6,8(2*H*,7*H*)-tetraone



C24 H12 N4 O4; Mol wt: 420.3828

ACTION – Anti-*Helicobacter pylori* agent for the treatment of gastric and duodenal ulcer and gastritis. Compound demonstrated *in vitro* activity against a panel of *H. pylori* strains with MICs of < 0.4 µg/ml and selectivity over other bacteria. *In vivo*, it almost completely eliminated *H. pylori* ATCC 43504 infection in mice treated at a dose of 20 mg/kg p.o. b.i.d. for 3 days. Other exemplified compounds are:



Compound	R1	R2	Formula
322157	Me	Me	C ₁₆ H ₁₀ N ₂ O ₄
322158	2-thiazolyl	2-thiazolyl	C ₂₀ H ₈ N ₄ O ₄ S ₂
322159	1,3-dioxo-2-isindolinyl	1,3-dioxo-2-isindolinyl	C ₃₀ H ₁₂ N ₄ O ₈
322160	(CH2)2OAc	(CH2)2OAc	C ₂₂ H ₁₈ N ₂ O ₈
322161	CH2CH2N(Me)2	CH2CH2N(Me)2	C ₂₂ H ₂₄ N ₄ O ₄

SOURCE – Shionogi.

REFERENCES

1. Sugimura, G. et al. (Shionogi & Co. Ltd.) *Anti-helicobacterial agents*. WO 0240479.

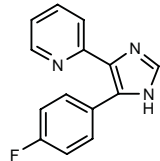
SOURCE – GlaxoSmithKline.

REFERENCES

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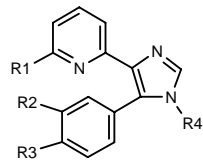
322004

2-[5-(4-Fluorophenyl)-1*H*-imidazol-4-yl]pyridine

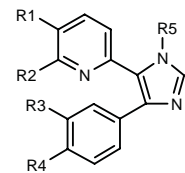


C14 H10 F N3; Mol wt: 239.2520

ACTION – An inhibitor of the transforming growth factor-β (TGF-β) signaling pathway that acts by inhibiting the phosphorylation of smad2 and smad3 by ALK5 kinase. Potentially useful for the treatment of chronic and acute renal diseases, wound healing, arthritis, osteoporosis, congestive heart failure, ulcers, ocular disorders, diabetic nephropathy, impaired neurological function, Alzheimer’s disease, atherosclerosis, fibrotic disorders and restenosis. Other exemplified compounds are:



Compound	R1	R2	R3	R4	Formula
322007	H	-OCH2O-	H	H	C ₁₅ H ₁₁ N ₃ O ₂
322008	Me	-OCH2O-	H	H	C ₁₆ H ₁₃ N ₃ O ₂
322009	Br	-OCH2O-	H	H	C ₁₅ H ₁₀ BrN ₃ O ₂
322011	Me	-OCH2CH2O-	H	H	C ₁₇ H ₁₅ N ₃ O ₂
322016	Me	-OCH2CH2O-	Me	H	C ₁₈ H ₁₇ N ₃ O ₂
322017	NHPh	-OCH2O-	H	H	C ₂₁ H ₁₆ N ₄ O ₂
322018	NHPh	H	F	H	C ₂₀ H ₁₅ FN ₄



Compound	R1	R2	R3	R4	R5	Formula
322014	-CH=CHCH=CH-	H	F	H	H	C ₁₈ H ₁₂ FN ₃
322015	H	Me	-OCH2CH2O-	Me	H	C ₁₈ H ₁₇ N ₃ O ₂

SOURCE – GlaxoSmithKline.

REFERENCES

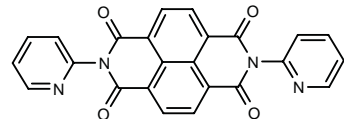
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GASTROINTESTINAL DRUGS

ANTIULCER DRUGS

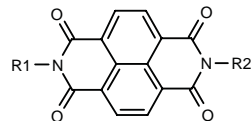
322156

2,7-Bis(2-pyridyl)benzo[*lmn*]-3,8-phenanthroline-1,3,6,8(2*H*,7*H*)-tetraone



C24 H12 N4 O4; Mol wt: 420.3828

ACTION – Anti-*Helicobacter pylori* agent for the treatment of gastric and duodenal ulcer and gastritis. Compound demonstrated *in vitro* activity against a panel of *H. pylori* strains with MICs of < 0.4 µg/ml and selectivity over other bacteria. *In vivo*, it almost completely eliminated *H. pylori* ATCC 43504 infection in mice treated at a dose of 20 mg/kg p.o. b.i.d. for 3 days. Other exemplified compounds are:



Compound	R1	R2	Formula
322157	Me	Me	C ₁₆ H ₁₀ N ₂ O ₄
322158	2-thiazolyl	2-thiazolyl	C ₂₀ H ₈ N ₄ O ₄ S ₂
322159	1,3-dioxo-2-isindolinyl	1,3-dioxo-2-isindolinyl	C ₃₀ H ₁₂ N ₄ O ₈
322160	(CH2)2OAc	(CH2)2OAc	C ₂₂ H ₁₈ N ₂ O ₈
322161	CH2CH2N(Me)2	CH2CH2N(Me)2	C ₂₂ H ₂₄ N ₄ O ₄

SOURCE – Shionogi.

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1. Sugimura, G. et al. (Shionogi & Co. Ltd.) *Anti-helicobacterial agents*. WO 0240479.

ENDOCRINE DRUGS

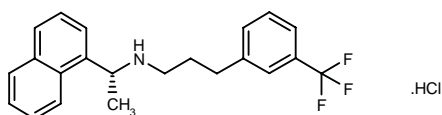
THYROID DISEASE THERAPY

CINACALCET HYDROCHLORIDE*

302362

N-[1(*R*)-(1-Naphthyl)ethyl]-*N*-[3-[3-(trifluoromethyl)-phenyl]propyl]amine hydrochloride

AMG-073.HCl



C22 H22 F3 N . HCl; Mol wt: 393.8777

ACTION – Calcimimetic proven to reduce parathyroid hormone (PTH) secretion and subsequently serum calcium by increasing the sensitivity of the parathyroid calcium-sensing receptor to extracellular calcium. Several clinical studies in patients with primary hyperparathyroidism showed that doses from 10 mg daily to 50 mg b.i.d. over up to 12 weeks significantly decreased serum calcium and PTH levels which were maintained over 1 year. No significant change was seen in the urine calcium/creatinine ratio, $1,25(\text{OH})_2\text{D}_3$ levels or bone mineral density. Compound was also associated with significant increases in bone-specific alkaline phosphatase and serum *N*-telopeptide compared with placebo. Other studies in hemodialysis patients with secondary hyperparathyroidism due to end-stage renal disease (ESRD) showed that compound lowered plasma PTH levels and serum calcium concentrations. It also improved several abnormalities in mineral metabolism implicated in vascular and soft tissue calcification and cardiovascular mortality in patients with ESRD by lowering serum phosphorus concentrations and the calcium-phosphorus ion product. Potentially useful for the treatment of hyperparathyroidism and currently in phase III trials.

SOURCES – Amgen; Kirin Brewery; NPS Pharmaceuticals.

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3. Dueke, T. et al. *Short-term treatment of secondary hyperparathyroidism (SHPT) with the calcimimetic agent AMG 073*. ASN/ISN World Congr Nephrol (Oct 13-17, San Francisco) 2001, Abst A3992.
4. Frazao, J.M. et al. *The calcimimetic agents: Perspectives for treatment*. Kidney Int 2002, 61(Suppl. 80): S149.
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11. Shoback, D.M. et al. *An evaluation of the calcimimetic AMG 073 in patients with hypercalcemia and primary hyperparathyroidism (PHPT)*. J Bone Miner Res 2001, 16(Suppl. 1): Abst SA462.

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15. *Amgen initiates phase III AMG-073 trial for hyperparathyroidism*. DailyDrugNews.com (Daily Essentials) 2001, Dec 27.

16. *Amgen reviews third quarter developments*. DailyDrugNews.com (Daily Essentials) 2000, Nov 17.

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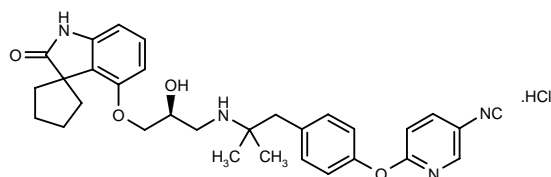
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*Identified compound **302362** (see **302359**) Drug Data Rep 2001, 023(08): 0826.

ANTIDIABETIC DRUGS

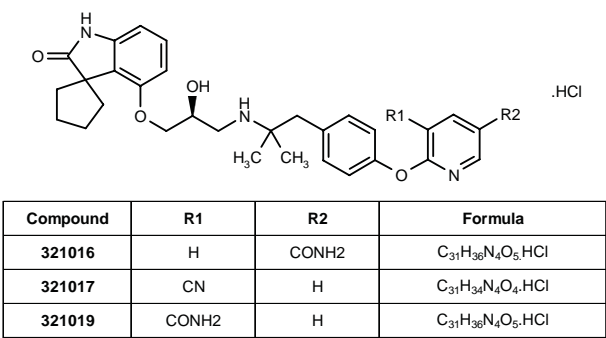
321015

6-[4-[2-[2(*S*)-Hydroxy-3-(2-oxo-2,3-dihydro-1*H*-spiro[indol-3,1'-cyclopentan]-4-yloxy)propylamino]-2-methylpropyl]phenoxy]pyridine-3-carbonitrile hydrochloride



C31 H34 N4 O4 . HCl; Mol wt: 563.0945

ACTION – β_3 -Adrenoceptor agonist exhibiting 49.9% of the activity of isoproterenol in the cAMP assay using CHO cells expressing human β_3 -adrenoceptor. Potentially useful for the treatment of type 2 diabetes and obesity. Other 3-substituted oxindole derivatives are:



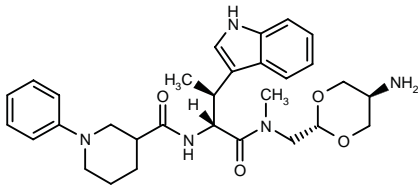
SOURCE – Lilly.

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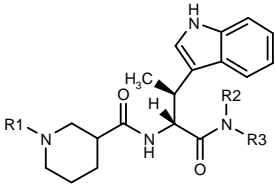
321156

trans-*N*¹-(5-Amino-1,3-dioxan-2-ylmethyl)-*N*¹,β(*S*)-dimethyl-*N*²-(1-phenylpiperidin-3-ylcarbonyl)-D-tryptophan-amide



C30 H39 N5 O4; Mol wt: 533.6691

ACTION – Selective somatostatin sst₂ receptor agonist, potentially useful for the treatment of diabetes, acromegaly, restenosis, retinopathy and depression. Other specifically claimed compounds are:



Compound	R1	R2	R3	Formula
321157	3-F-PhCH2	trans-5-NH2- -1,3-dioxan-2-yl-CH2	Me	C ₃₁ H ₄₀ FN ₅ O ₄
321158	3,5-(F)2-PhCH2CO	CH(CO2-t-Bu)(CH2)4NH2	H	C ₃₆ H ₄₇ F ₂ N ₅ O ₅

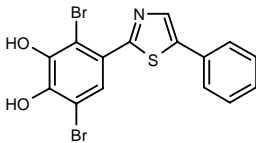
SOURCE – Merck & Co.

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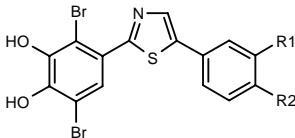
321178

3,6-Dibromo-4-(5-phenylthiazol-2-yl)benzene-1,2-diol

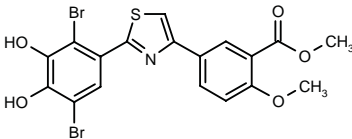


C15 H9 Br2 N O2 S; Mol wt: 427.1151

ACTION – Protein-tyrosine-phosphatase PTP1B inhibitor (IC₅₀ = 0.54 μM) with blood glucose-lowering effects in mice administered an oral dose of 3 mg/kg/day for 5 days (45 and 44% decrease in blood glucose levels at 3-4 and 8-9 h after administration, respectively). Potentially useful for the treatment of diabetes. Other exemplified compounds are:



Compound	R1	R2	Formula
321179	H	CO2H	C ₁₆ H ₉ Br ₂ NO ₄ S
321180	CO2H	H	C ₁₆ H ₉ Br ₂ NO ₄ S



321181: C18 H13 Br2 N O5 S

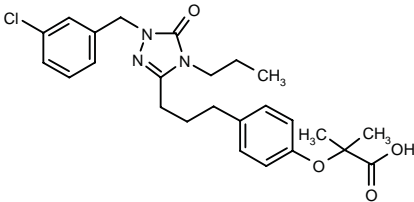
SOURCE – Japan Tobacco.

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1. Inaba, T. et al. (Japan Tobacco Inc.) *2-(2,5-Dihalogen-3,4-dihydroxyphenyl)azole cpds. and medicinal compsns. containing them*. JP 2002114768.

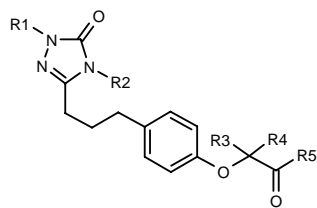
321286

2-[4-[3-[1-(3-Chlorobenzyl)-5-oxo-4-propyl-4,5-dihydro-1*H*-1,2,4-triazol-3-yl]propyl]phenoxy]-2-methylpropionic acid



C25 H30 Cl N3 O4; Mol wt: 471.9820

ACTION – Peroxisome proliferator-activated receptor PPARα agonist, potentially useful for the treatment of diabetes, cardiovascular disorders, syndrome X and obesity. Other exemplified compounds include the following:



Compound	R1	R2	R3	R4	R5	Formula
321287	4-t-Bu-PhCH2	Et	Me	Me	NH2	C ₂₈ H ₃₈ N ₄ O ₃
321288	4-t-Bu-PhCH2	Me	Me	4-F-PhCH2	OH	C ₃₃ H ₃₈ FN ₃ O ₄
321289	3,4-(Me)2-PhCH2	Pr	H	C5H11	OH	C ₃₀ H ₄₁ N ₃ O ₄
321290	3-Cl-PhCH2	H	Me	Me	OH	C ₂₂ H ₂₄ ClN ₃ O ₄
321291	3,4-(Me)2-PhCH2	Pr	-(CH2)3-	Me	OH	C ₂₈ H ₃₅ N ₃ O ₄
321292	4-Me-PhCH2	Pr	Me	Me	OEt	C ₂₈ H ₃₇ N ₃ O ₄
321293	4-CF3-Ph	2-F-Ph-CH2CH2	Me	Me	OH	C ₃₀ H ₂₉ F ₄ N ₃ O ₄
321294	cyclohexyl-CH2NHCOCH2	Et	Me	Me	OH	C ₂₆ H ₃₈ N ₄ O ₅

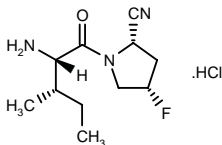
SOURCE – Lilly.

REFERENCES

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321359

4(S)-Fluoro-1-(L-isoleucyl)pyrrolidine-2(S)-carbonitrile hydrochloride



C11 H18 F N3 O . HCl; Mol wt: 263.7421

ACTION – Dipeptidyl-peptidase IV (DPP-IV) inhibitor (IC₅₀ = 0.6 nM) reported to significantly attenuate the increase in blood glucose levels in rats subjected to an oral glucose tolerance test. Potentially useful for the treatment of type 2 diabetes, immune disorders such as transplant rejection, arthritis, obesity, osteoporosis, benign prostatic hyperplasia and dermatopathy. Further applications include inflammatory enteropathy, multiple sclerosis, rheumatoid arthritis, AIDS and cancer metastasis.

SOURCE – Taisho.

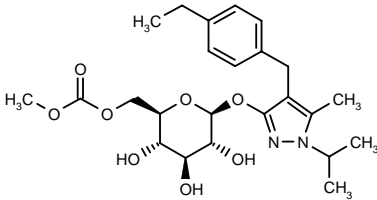
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321531

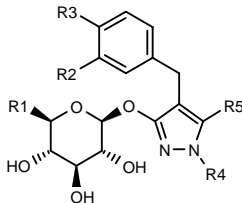
4-(4-Ethylbenzyl)-1-isopropyl-5-methyl-1 H-pyrazol-3-yl 6-O-(methoxycarbonyl)-β-D-glucopyranoside

1-O-[4-(4-Ethylbenzyl)-1-isopropyl-5-methyl-1 H-pyrazol-3-yl]-β-D-glucopyranos-6-O-yl methyl carbonate



C24 H34 N2 O8; Mol wt: 478.5386

ACTION – An inhibitor of the sodium-dependent glucose transporter SGLT2 that was shown to dose-dependently increase urinary glucose excretion following oral administration to rats at doses of 3-100 mg/kg. Potentially useful for the treatment of diabetes. Other exemplified pyrazole derivatives are:



Compound	R1	R2	R3	R4	R5	Formula
321532	CO2H	H	Et	H	CF3	C ₁₉ H ₂₁ F ₃ N ₂ O ₇
321533	CH2OCO2Me	H	Et	CH2Ph	CF3	C ₂₈ H ₃₁ F ₃ N ₂ O ₈
321536	CH2OCO2Me	H	Et	4-MeO-PhCH2	CF3	C ₂₉ H ₃₃ F ₃ N ₂ O ₉
321537	CH2OCO2Me	H	Et	Ph	CF3	C ₂₇ H ₂₉ F ₃ N ₂ O ₈
321538	CH2OCO2Me	F	OMe	i-Pr	Me	C ₂₃ H ₃₁ FN ₂ O ₉
321539	CH2OCO2Me	F	Me	i-Pr	Me	C ₂₃ H ₃₁ FN ₂ O ₈
321541	CH2OH	H	SMe	H	CF3	C ₁₈ H ₂₁ F ₃ N ₂ O ₆ S

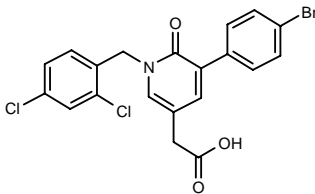
SOURCE – Ajinomoto.

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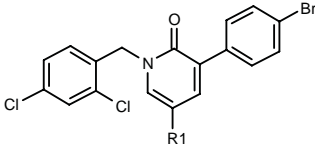
321706

2-[5-(4-Bromophenyl)-1-(2,4-dichlorobenzyl)-6-oxo-1,6-dihydropyridin-3-yl]acetic acid



C20 H14 Br Cl2 N O3; Mol wt: 467.1446

ACTION – An inhibitor of adipocyte fatty binding protein aP2, a protein involved in the regulation of fatty acid trafficking in adipocytes. Potentially useful for the treatment of type 2 diabetes, insulin resistance, hyperglycemia, hyperinsulinemia, obesity, hypertriglyceridemia, inflammation, atherosclerosis, diabetic retinopathy, diabetic neuropathy and diabetic nephropathy. Other specifically claimed pyridone derivatives are:



Compound	R1	Formula
321707	CO2Et	C ₂₁ H ₁₆ BrCl ₂ NO ₃
321708	CO2H	C ₁₉ H ₁₂ BrCl ₂ NO ₃
321709	CH2OH	C ₁₉ H ₁₄ BrCl ₂ NO ₂

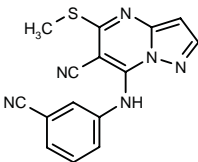
SOURCE – Bristol-Myers Squibb.

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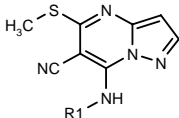
321734

7-(3-Cyanophenylamino)-5-(methylsulfanyl)pyrazolo-[1,5-a]pyrimidine-6-carbonitrile



C15 H10 N6 S; Mol wt: 306.3520

ACTION – Glucose uptake activator shown to increase glucose uptake in rat skeletal muscle L6 cells by > 15% with respect to controls at 10 µg/ml. In a mouse model of type 2 diabetes, compound demonstrated blood glucose-lowering effects following oral administration at a dose of 50 mg/kg. Potentially useful for the treatment of impaired glucose tolerance and diabetic complications including angiopathy, retinopathy, nephropathy, neuropathy and hypertension, as well as for the treatment of obesity. Other exemplified compounds are:



Compound	R1	Formula
321735	4-Pyr-CH2	C ₁₄ H ₁₂ N ₆ S
321736	2-dioxolanyl-CH2	C ₁₂ H ₁₃ N ₅ O ₂ S
321737	4-Me-PhCH2	C ₁₆ H ₁₅ N ₅ S
321738	4-NO2-Ph	C ₁₄ H ₁₀ N ₆ O ₂ S

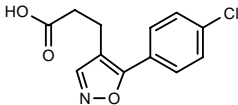
SOURCE – Ishihara Sangyo.

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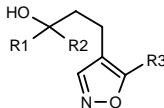
321902

3-[5-(4-Chlorophenyl)isoxazol-4-yl]propionic acid



C12 H10 Cl N O3; Mol wt: 251.6680

ACTION – Antidiabetic agent shown to stimulate insulin secretion in rat pancreatic Langerhans islets by 256% at 100 µM and proven to lower blood glucose levels by 15% with respect to controls when administered to rats at 30 mg/kg orally. Other exemplified isoxazole derivatives are:



Compound	R1	R2	R3	Formula
321903	H	H	4-Cl-Ph	C ₁₂ H ₁₂ ClNO ₂
321904	H	H	4-F-Ph	C ₁₂ H ₁₂ FNO ₂
321905	H	H	5-Cl-2-thienyl	C ₁₀ H ₁₀ ClNO ₂ S
321906	H	H	3,4-(Cl)2-Ph	C ₁₂ H ₁₁ Cl ₂ NO ₂
321907		-O-	3,4-(Cl)2-Ph	C ₁₂ H ₉ Cl ₂ NO ₃
321908	H	H	3,4-(F)2-Ph	C ₁₂ H ₁₁ F ₂ NO ₂
321909	H	H	3-Cl-4-F-Ph	C ₁₂ H ₁₁ ClFNO ₂
321911		-O-	4,5-(Cl)2-2-thienyl	C ₁₀ H ₇ Cl ₂ NO ₃ S
321912		-O-	5-Cl-2-thienyl	C ₁₀ H ₉ ClNO ₃ S
321913		-O-	3,4-(F)2-Ph	C ₁₂ H ₉ F ₂ NO ₃
321914		-O-	3-Cl-4-F-Ph	C ₁₂ H ₉ ClFNO ₃

SOURCE – Takeda.

REFERENCES

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321928

Glycyl-L-isoleucyl-L-valyl-L-glutamyl-L-glutaminyl-L-cysteinyl-L-seryl-L-threonyl-L-seryl-L-isoleucyl-L-cysteinyl-L-seryl-L-leucyl-L-tyrosyl-L-glutaminyl-L-leucyl-L-glutamyl-L-asparaginyl-L-tyrosyl-L-seryl-L-asparagine S-3.6-S-3.11-disulfide

C99 H153 N25 O37 S2; Mol wt: 2349.5680

ACTION – Insulin A-chain analogue proven to be as efficient as insulin on stimulating DNA synthesis, glucose uptake and glycogen formation, as demonstrated in *in vitro* cell systems. Potentially useful for the treatment of diabetes.

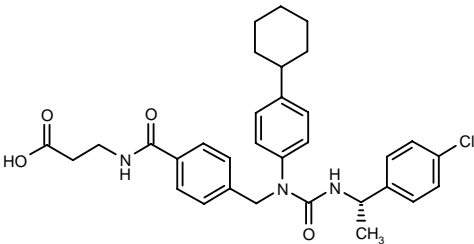
SOURCES – Université de Bourdeaux, Bourdeaux (FR); Université de Caen, Caen Cedex (FR); Université de Picardie Jules Verne, Amiens (FR).

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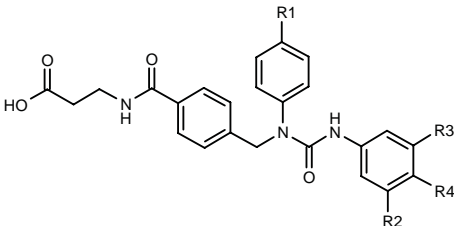
321949

3-[4-[3-[1(*S*)-(4-Chlorophenyl)ethyl]-1-(4-cyclohexylphenyl)ureidomethyl]benzamido]propionic acid



C32 H36 Cl N3 O4; Mol wt: 562.1064

ACTION – Glucagon antagonist, potentially useful for the treatment of hyperglycemia, impaired glucose tolerance, type 1 and type 2 diabetes and obesity. Other exemplified compounds are:



Compound	R1	R2	R3	R4	Formula
321950	1-cyclohexenyl	H	Br	H	C ₃₀ H ₃₀ BrN ₃ O ₄
321951	1-cyclohexenyl	H	OCF3	H	C ₃₁ H ₃₀ F ₃ N ₃ O ₅
321952	cyclohexyl	F	CF3	H	C ₃₁ H ₃₁ F ₄ N ₃ O ₄
321953	cyclohexyl	H	Br	H	C ₃₀ H ₃₂ BrN ₃ O ₄
321954	cyclohexyl	H	CF3	H	C ₃₁ H ₃₂ F ₃ N ₃ O ₄
321955	1-cyclohexenyl	CN	CF3	H	C ₃₂ H ₂₉ F ₃ N ₄ O ₄
321956	cyclohexyl	H	CH2OH	OCF3	C ₃₂ H ₃₄ F ₃ N ₃ O ₆
321957	1-cyclohexenyl	H	CH2OH	OCF3	C ₃₂ H ₃₂ F ₃ N ₃ O ₆

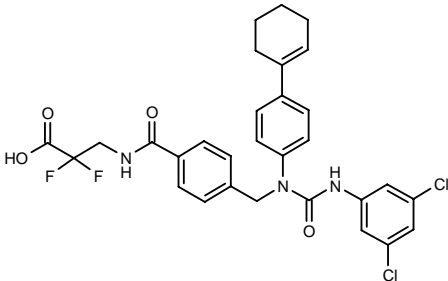
SOURCES – Agouron (Pfizer); Novo Nordisk.

REFERENCES

1. Madsen, P. et al. (Novo Nordisk A/S;Agouron Pharmaceuticals, Inc.) *Glucagon antagonists/inverse agonists.* WO 0240444.

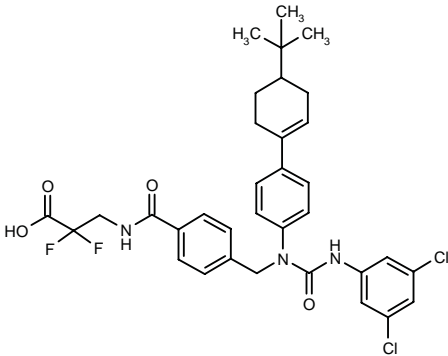
321968

3-[4-[1-[4-(1-Cyclohexen-1-yl)phenyl]-3-(3,5-dichlorophenyl)ureidomethyl]benzamido]-2,2-difluoropropionic acid



C30 H27 Cl2 F2 N3 O4; Mol wt: 602.4623

ACTION – Glucagon antagonist, potentially useful for the treatment of hyperglycemia, impaired glucose tolerance, type 1 and type 2 diabetes and obesity. Another exemplified compound is:



321969: C34 H35 Cl2 F2 N3 O4

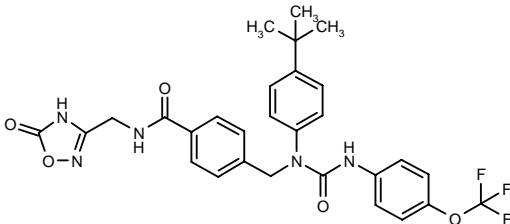
SOURCE – Novo Nordisk.

REFERENCES

1. Joergensen, A.S. and Madsen, P. (Novo Nordisk A/S) *Glucagon antagonist/inverse agonist.* WO 0240446.

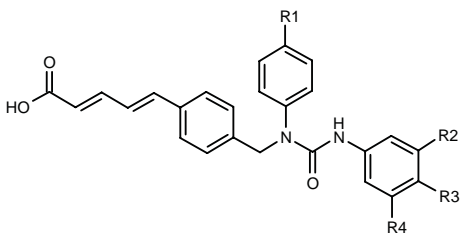
321971

4-[1-(4-*tert*-Butylphenyl)-3-[4-(trifluoromethoxy)phenyl]-ureidomethyl]-*N*-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-ylmethyl)benzamide

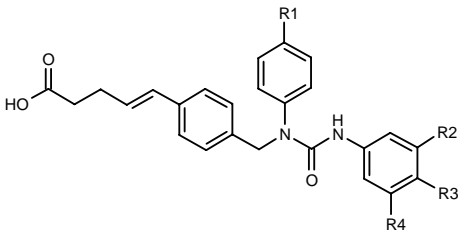


C29 H28 F3 N5 O5; Mol wt: 583.5642

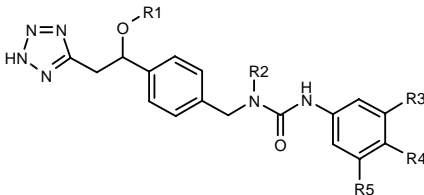
ACTION – Glucagon antagonist, potentially useful for the treatment of hyperglycemia, impaired glucose tolerance, type 1 and type 2 diabetes and obesity. Other exemplified compounds are:



Compound	R1	R2	R3	R4	Formula
321972	t-Bu		-CF2OCF2O-	H	C ₃₁ H ₂₈ F ₄ N ₂ O ₅
321973	t-Bu	CF3	H	CF3	C ₃₁ H ₂₈ F ₆ N ₂ O ₃
321974	1-cyclohexenyl	CF3	H	CF3	C ₃₃ H ₂₈ F ₆ N ₂ O ₃



Compound	R1	R2	R3	R4	Formula
321975	t-Bu	H	OCF3	H	C ₃₀ H ₃₁ F ₃ N ₂ O ₄
321977	1-cyclohexenyl	Cl	H	Cl	C ₃₁ H ₃₀ Cl ₂ N ₂ O ₃



Compound	R1	R2	R3	R4	R5	Formula
321978	H	4-t-Bu-cyclohexyl	H	OCF3	H	C ₂₈ H ₃₅ F ₃ N ₆ O ₃
321979	H	4-t-Bu-cyclohexyl	CF3	H	CF3	C ₂₉ H ₃₄ F ₆ N ₆ O ₂
321980	Ac	4-(cyclohexenyl)-Ph	Cl	H	Cl	C ₃₁ H ₃₀ Cl ₂ N ₆ O ₃

SOURCE – Novo Nordisk.

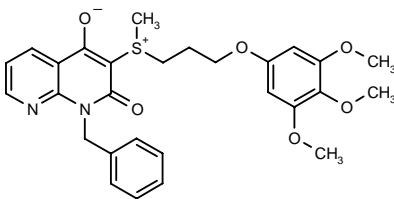
REFERENCES

1. Behrens, C. et al. (Novo Nordisk A/S) *Glucagon antagonists/inverse agonists*. WO 0240445.

TREATMENT OF DIABETIC COMPLICATIONS

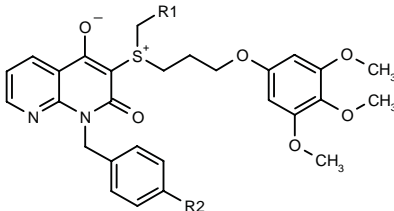
321335

1-Benzyl-3-[methyl[3-(3,4,5-trimethoxyphenoxy)propyl]-sulfonio]-2-oxo-1,2-dihydro-1,8-naphthyridin-4-olate



C28 H30 N2 O6 S; Mol wt: 522.6190

ACTION – Analgesic agent for use in the treatment of diabetic neuropathy and also able to potentiate adenosine. The compound demonstrated *in vivo* activity in a rat model of diabetic neuropathy at a dose of 30 mg/kg p.o. Other exemplified 1,8-naphthyridin-4-olate derivatives are:



Compound	R1	R2	Formula
321336	H	OMe	C ₂₉ H ₃₂ N ₂ O ₇ S
321337	Me	H	C ₂₉ H ₃₂ N ₂ O ₆ S

SOURCE – Otsuka.

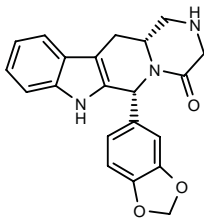
REFERENCES

1. Shibuya, T. (Otsuka Pharmaceutical Co., Ltd.) *Naphthyridine derivs.* JP 2002138089.

TREATMENT OF MALE SEXUAL DYSFUNCTION

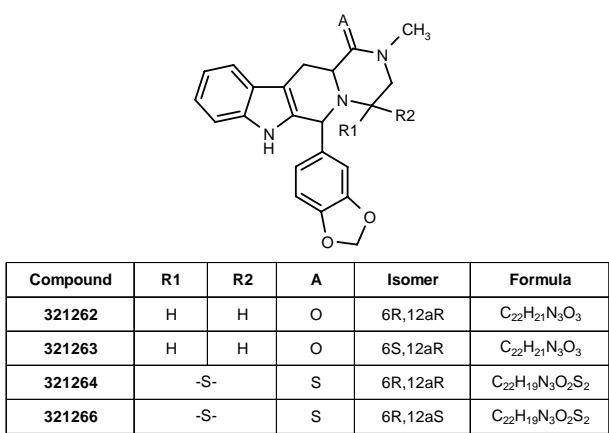
321260

(6*R*,12*aR*)-6-(1,3-Benzodioxol-5-yl)-1,2,3,4,6,7,12,12a-octahydropyrazino[1',2':1,6]pyrido[3,4-*b*]indol-4-one



C21 H19 N3 O3; Mol wt: 361.3991

ACTION – Phosphodiesterase type 5 (PDE5) inhibitor (IC₅₀ = 2.3 nM) potentially useful for the treatment of male erectile dysfunction and female arousal disorder. Compound is also described as useful for the treatment of angina pectoris, pulmonary hypertension, chronic obstructive pulmonary disease, hypertension, acute respiratory distress syndrome, congestive heart failure, renal failure, atherosclerosis, inflammation, myocardial infarction, stroke and asthma, among other disorders. Other specifically claimed indole derivatives are:



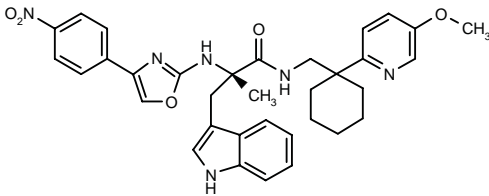
SOURCE – Lilly Icos.

REFERENCES

1. Orme, M.W. et al. (Lilly Icos LLC) *Indole derivs. as PDE5-inhibitors*. WO 0236593.

321777

3-(1*H*-Indol-3-yl)-*N*-[1-(5-methoxypyridin-2-yl)cyclohexylmethyl]-2(*S*)-methyl-2-[4-(4-nitrophenyl)oxazol-2-ylamino]propionamide



C34 H36 N6 O5; Mol wt: 608.6954

ACTION – Bombesin receptor antagonist displaying K_i values of 4 and 24 nM, respectively, in bombesin BB1 and BB2 receptor binding assays. Compound also demonstrated *in vivo* activity in rat models of female sexual proceptivity and receptivity following oral administration. Potentially useful for the treatment of male and female sexual dysfunction, as well as anxiety, panic, depression, sleep disorders, memory impairment, pulmonary hypertension, cancer, hepatic porphyria, gastrointestinal disorders including colitis, Crohn’s disease and inflammatory bowel disease, emesis, anorexia, pain, seasonal affective disorders, eating disorders and pruritus.

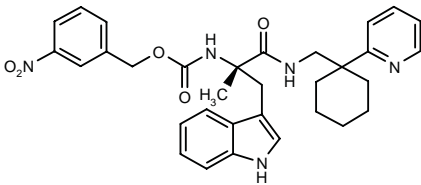
SOURCE – Pfizer.

REFERENCES

1. Higginbottom, M. et al. (Pfizer Inc.) *Bombesin receptor antagonists*. WO 0240475.

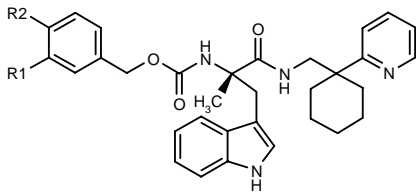
321780

N-[2-(1*H*-Indol-3-yl)-1(*S*)-methyl-1-[*N*-[1-(2-pyridyl)cyclohexylmethyl]carbamoyl]ethyl]carbamic acid 3-nitrobenzyl ester



C32 H35 N5 O5; Mol wt: 569.6585

ACTION – Bombesin receptor antagonist displaying IC₅₀ values of 17 and 612 nM, respectively, at bombesin BB1 and BB2 receptors. Potentially useful for the treat-ment of male and female sexual dysfunction, as well as anxiety, panic, depression, sleep disorders, memory impairment, pulmonary hypertension, cancer, hepatic porphyria, gastrointestinal disorders including colitis, Crohn’s disease and inflammatory bowel disease, emesis, anorexia, pain, seasonal affective disorders, eating disorders and pruritus. Other exemplified compounds are:



Compound	R1	R2	Formula
321781	H	NO2	C ₃₂ H ₃₅ N ₅ O ₅
321782	CN	H	C ₃₃ H ₃₅ N ₅ O ₃

SOURCE – Pfizer.

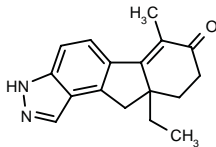
REFERENCES

1. Higginbottom, M. et al. (Pfizer Inc.) *Bombesin receptor antagonists*. WO 0240469.

TREATMENT OF GYNECOLOGICAL DISORDERS

322044

9a-Ethyl-6-methyl-3,7,8,9,9a,10-hexahydroindeno[2,1-*e*]-indazol-7-one



C17 H18 N2 O; Mol wt: 266.3422

ACTION – A representative compound from a series of estrogen receptor modulators, reported to be useful for the treatment of a variety of estrogen-related disorders, particularly hot flashes.

SOURCE – Merck & Co.

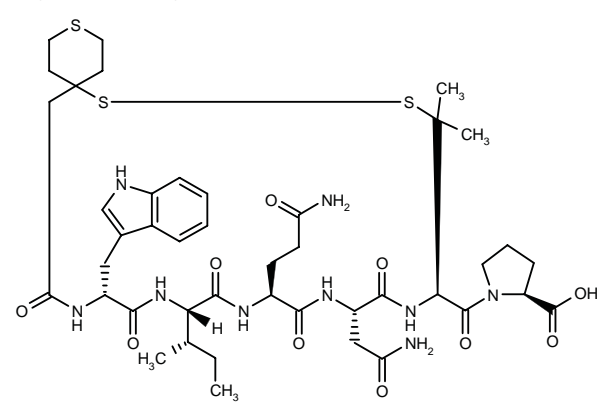
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1. Wilkening, R.R. et al. (Merck & Co., Inc.) *Estrogen receptor modulators*. WO 0241835.

UTERINE STIMULANTS
AND TOCOLYTICS

321356

N-[2-(4-Sulfanyltetrahydrothiopyran-4-yl)acetyl]-D-tryptophyl-L-isoleucyl-L-glutaminyl-L-asparaginyl-L-penicillaminyl-L-proline cyclic disulfide



C43 H61 N9 O10 S3; Mol wt: 960.2059

ACTION – Cyclic peptide oxytocin receptor antagonist, potentially useful for the treatment of preterm labor. This compound inhibited oxytocin-stimulated contractions in rat uterine muscle with an IC₅₀ of 25.0 nM, while inducing only 30% relaxation of arginine vasopressin (AVP)-constricted rat aorta at a concentration of 10 μM (> 400-fold selectivity over vasopressin V_{1a} receptors).

SOURCE – Mitsubishi Pharma.

REFERENCES

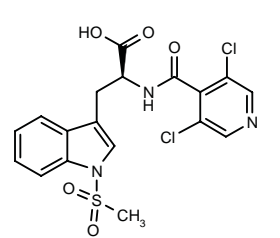
1. Kamiya, S. et al. (Mitsubishi Pharma Corp.) *Peptidic cpds., and medicinal compsns. containing them*. JP 2002138098.

DERMATOLOGIC DRUGS

ANTIPSORIATICS

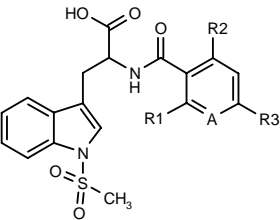
321632

2-(S)-(3,5-Dichloropyridin-4-ylcarboxamido)-3-[1-(methylsulfonyl)-1H-indol-3-yl]propionic acid

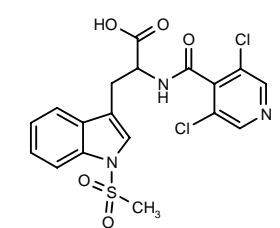


C18 H15 Cl2 N3 O5 S; Mol wt: 456.3045

ACTION – Agent with the ability to inhibit the interaction between lymphocyte function-associated antigen-1 (LFA-1) and intracellular adhesion molecule-1 (ICAM-1). Potentially useful for the treatment of inflammatory and hyperproliferative skin disorders such as psoriasis, atopic dermatitis, allergic and irritant contact dermatitis, and eczematous or seborrheic dermatitis. Other exemplified compounds are:



Compound	R1	R2	R3	A	Isomer	Formula
321634	Cl	Cl	H	CH	S	C ₁₉ H ₁₆ Cl ₂ N ₃ O ₅ S
321635	Cl	H	H	N	S	C ₁₈ H ₁₆ ClN ₃ O ₅ S
321637	H	Cl	3-OH-PhCH ₂ NHCO	CH		C ₂₇ H ₂₄ ClN ₃ O ₇ S
322638	Cl	Cl	H	CH		C ₁₉ H ₁₆ Cl ₂ N ₃ O ₅ S



321640: C18 H15 Cl2 N3 O5 S

SOURCE – Celltech Group.

REFERENCES

1. Archibald, S.C. et al. (Celltech Group plc) *1-Sulfonyl substd. tryptophan derivs. and its use as integrin inhibitors*. WO 0242294.

SOURCE – Merck & Co.

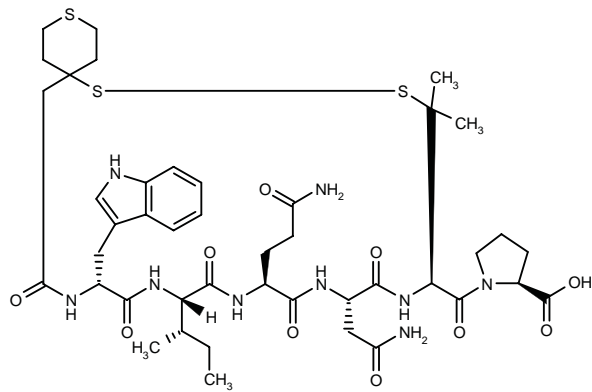
REFERENCES

1. Wilkening, R.R. et al. (Merck & Co., Inc.) *Estrogen receptor modulators*. WO 0241835.

UTERINE STIMULANTS
AND TOCOLYTICS

321356

N-[2-(4-Sulfanyltetrahydrothiopyran-4-yl)acetyl]-D-tryptophyl-L-isoleucyl-L-glutaminy-L-asparaginy-L-penicillaminy-L-proline cyclic disulfide



C43 H61 N9 O10 S3; Mol wt: 960.2059

ACTION – Cyclic peptide oxytocin receptor antagonist, potentially useful for the treatment of preterm labor. This compound inhibited oxytocin-stimulated contractions in rat uterine muscle with an IC₅₀ of 25.0 nM, while inducing only 30% relaxation of arginine vasopressin (AVP)-constricted rat aorta at a concentration of 10 μM (> 400-fold selectivity over vasopressin V_{1a} receptors).

SOURCE – Mitsubishi Pharma.

REFERENCES

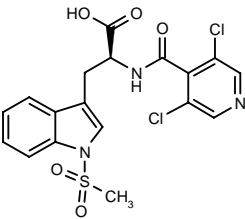
1. Kamiya, S. et al. (Mitsubishi Pharma Corp.) *Peptidic cpds., and medicinal compsns. containing them*. JP 2002138098.

DERMATOLOGIC DRUGS

ANTIPSORIATICS

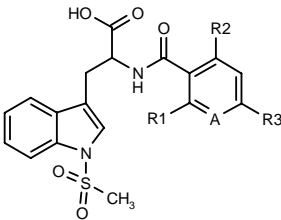
321632

2-(S)-(3,5-Dichloropyridin-4-ylcarboxamido)-3-[1-(methylsulfonyl)-1H-indol-3-yl]propionic acid

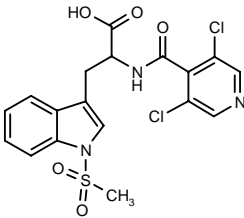


C18 H15 Cl2 N3 O5 S; Mol wt: 456.3045

ACTION – Agent with the ability to inhibit the interaction between lymphocyte function-associated antigen-1 (LFA-1) and intracellular adhesion molecule-1 (ICAM-1). Potentially useful for the treatment of inflammatory and hyperproliferative skin disorders such as psoriasis, atopic dermatitis, allergic and irritant contact dermatitis, and eczematous or seborrheic dermatitis. Other exemplified compounds are:



Compound	R1	R2	R3	A	Isomer	Formula
321634	Cl	Cl	H	CH	S	C ₁₉ H ₁₆ Cl ₂ N ₃ O ₅ S
321635	Cl	H	H	N	S	C ₁₈ H ₁₆ ClN ₃ O ₅ S
321637	H	Cl	3-OH-PhCH2NHCO	CH		C ₂₇ H ₂₄ ClN ₃ O ₇ S
322638	Cl	Cl	H	CH		C ₁₉ H ₁₆ Cl ₂ N ₃ O ₅ S



321640: C18 H15 Cl2 N3 O5 S

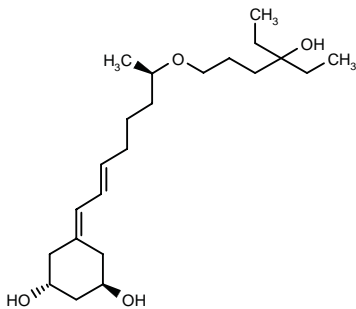
SOURCE – Celltech Group.

REFERENCES

1. Archibald, S.C. et al. (Celltech Group plc) *1-Sulfonyl substd. tryptophan derivs. and its use as integrin inhibitors*. WO 0242294.

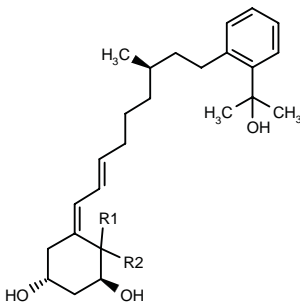
321651

5-[7(*R*)-(4-Ethyl-4-hydroxyhexyloxy)-2(*E*)-octenyldene]-cyclohexane-1(*R*),3(*R*)-diol

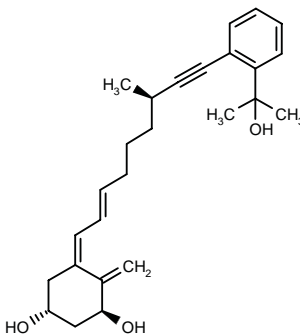


C22 H40 O4; Mol wt: 368.5540

ACTION – Vitamin D analogue for use in the treatment of hyperproliferative skin disorders including psoriasis, basal cell carcinoma, disorders of keratinization and keratosis, and conditions associated with photodamage. Compound was well tolerated in mice, with no increase in body weight (highest tolerated dose [HTD] > 5000 µg/kg s.c.), suggesting no change in calcium homeostasis. Other exemplified retiferol derivatives are.



Compound	R1	R2	Formula
321652	-CH2-		C ₂₆ H ₃₈ O ₃
321653	H	H	C ₂₅ H ₃₈ O ₃



321654: C26 H34 O3

SOURCE – Roche.

REFERENCES

1. Barbier, P. et al. (F. Hoffmann-La Roche AG) *Retiferol derivs. and their use in the treatment of skin diseases or conditions associated with photodamage*. WO 0242247.

SIPLIZUMAB

USAN

250466

Immunoglobulin G₁, anti-(human CD2 [antigen]) (human-rat monoclonal MEDI-507 γ₁-chain), disulfide with human-rat monoclonal MEDI-507 light chain, dimer

MEDI-507

ACTION – Immunomodulator, a humanized anti-CD22 human monoclonal antibody that selectively suppresses the function of T- and natural killer (NK) cells via a nonapoptotic cytotoxic mechanism. Results of phase I and I/II clinical studies in patients with moderate to severe psoriasis showed that compound given as a single i.v. infusion (0.4-40 µg/kg), 8 weekly i.v. infusions (1.2-40 µg/kg) or 12 weekly s.c. injections (0.7-7.0 mg/kg) was well tolerated with only mild and transient adverse effects, including chills, headache, reduced heart rate and injection site reaction. At the highest doses (40 µg/kg i.v and 7 mg/kg s.c.), more than 55 and 33% of the patients showed at least 50 and 75% improvement in Psoriasis Area and Severity Index (PASI) scores, respectively. Overall, 70% of the patients exhibited an improvement in the PASI score of 25% or greater. Results of a phase I/II clinical trial in patients with steroid-naïve, severe graft-versus-host disease (GvHD) showed that the compound in combination with steroid therapy was well tolerated and effective in preventing GvHD. Compound is undergoing phase II testing for the treatment of psoriasis and prevention of GvHD.

SOURCES – BioTransplant; Katholieke Universiteit Leuven, Leuven (BE); MedImmune.

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8. McCall, C. et al. *Subcutaneous injection of MEDI-507, an anti-T-cell monoclonal antibody, for the treatment of psoriasis: Phase I results*. J Invest Dermatol 2001, 117(3): Abst 309.

9. Papp, K. et al. *Safety, tolerance, and disease activity of MEDI-507 (siplizumab) for the treatment of moderate to severe psoriasis*. 60th Annu Meet Am Acad Dermatol (Feb 22-27, New Orleans) 2002, Abst P23.

10. Spitzer, T.R. et al. *Durable progression free survival (PFS) following non-myeloablative bone marrow transplantation (BMT) for chemorefractory diffuse large B cell lymphoma (B-LCL)*. Blood 2001, 98(11, Part 1): Abst 2813.

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19. *MedImmune and BioTransplant plan to test MEDI-507 for graft-vs.-host disease*. DailyDrugNews.com (Daily Essentials) 1997, Dec 29.

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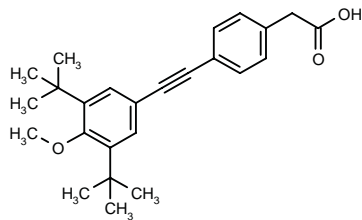
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MISCELLANEOUS DERMATOLOGIC DRUGS

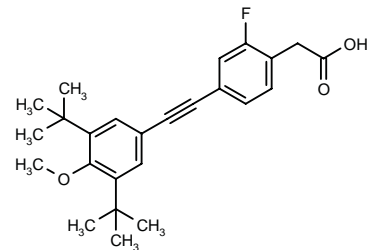
321187

2-[4-(3,5-Di-*tert*-butyl-4-methoxyphenylethynyl)phenyl]-acetic acid



C25 H30 O3; Mol wt: 378.5090

ACTION – Agent with the ability to inhibit retinoic acid-inducible cytochrome P-450 (P-450RAI), potentially useful for the treatment of a broad range of disorders, i.e., skin disorders such as keratoses, acne, psoriasis and atopic dermatitis, microbial infections, type 2 diabetes, cancer, ocular diseases such as proliferative vitreoretinopathy, retinal detachment and dry eye, dyslipidemia, post-angioplasty restenosis, human papillomavirus infections, inflammatory conditions such as pulmonary fibrosis, ileitis, colitis and Crohn’s disease, Alzheimer’s disease, Parkinson’s disease, stroke, immune disorders, transplant rejection and wound healing. Another specifically claimed compound is:



321188: C25 H29 F O3

SOURCE – Allergan.

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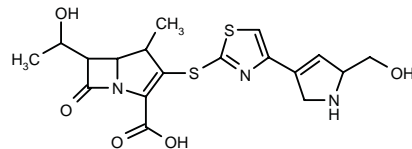
1. Vasudevan, J. et al. (Allergan, Inc.) *Cpds. having activity as inhibitors of cytochrome P450RAI*. US 6387951.

ANTIINFECTIVE THERAPY

ANTIBIOTICS

321453

6-(1-Hydroxyethyl)-2-[4-[5-(hydroxymethyl)-2,5-dihydro-1*H*-pyrrol-3-yl]thiazol-2-ylsulfanyl]-1-methyl-1-carba-2-penem-3-carboxylic acid



C18 H21 N3 O5 S2; Mol wt: 423.5119

ACTION – Carbapenem antibiotic, particularly useful for the treatment of infections caused by methicillin-resistant *Staphylococcus aureus* and methicillin-resistant coagulase-negative staphylococcal strains. Other exemplified β -lactams are:

11. Spitzer, T.R. et al. *Haploidentical donor bone marrow transplantation (BMT) for advanced hematologic malignancy (HM) following non-myeloablative preparative therapy: Role of in vivo T-cell depletion with anti-thymocyte globulin or anti-CD2 monoclonal antibody therapy (MEDI-507)*. Blood 2000, 96(11, Part 1): Abst 3633.

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15. *Final phase I/II clinical data presented at European psoriasis meeting for siplizumab*. DailyDrugNews.com (Daily Essentials) 2001, Dec 30.

16. *International Psoriasis Symposium selected by MedImmune to present phase I results for MEDI-507*. DailyDrugNews.com (Daily Essentials) 2001, June 26.

17. *MEDI-507 enters phase II evaluation in patients with psoriasis*. DailyDrugNews.com (Daily Essentials) 2001, April 4.

18. *MedImmune and BioTransplant initiate two new clinical studies of MEDI-507*. DailyDrugNews.com (Daily Essentials) 1998, Dec 16.

19. *MedImmune and BioTransplant plan to test MEDI-507 for graft-vs.-host disease*. DailyDrugNews.com (Daily Essentials) 1997, Dec 29.

20. *MedImmune and BioTransplant submit IND to begin first human clinical trial with MEDI-507*. MedImmune, Inc. Press Release 1997, April 15.

21. *MedImmune begins additional study of siplizumab in psoriasis patients*. DailyDrugNews.com (Daily Essentials) 2001, July 27.

22. *MedImmune expands phase II development of MEDI-507 to include Europe*. DailyDrugNews.com (Daily Essentials) 2001, June 8.

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24. *MedImmune seeks FDA approval for psoriasis trials with MEDI-507*. DailyDrugNews.com (Daily Essentials) 1997, Nov 28.

25. *Orphan drug designation granted to MEDI-507 for use in AlloMune system*. DailyDrugNews.com (Daily Essentials) 1998, Oct 16.

26. *Patient enrollment completed in trials for MedImmune humanized monoclonal antibodies*. DailyDrugNews.com (Daily Essentials) 2002, Jan 2.

27. *Phase I/II data presented for MEDI-507 in steroid-resistant GvHD*. DailyDrugNews.com (Daily Essentials) 1999, July 15.

28. *Positive phase I/II AlloMune results for end-stage lymphoma*. DailyDrugNews.com (Daily Essentials) 2001, Dec 31.

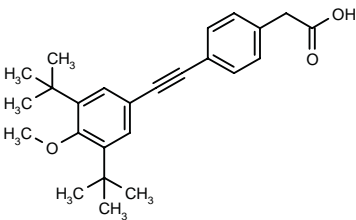
29. *Safety and pharmacokinetic data reported for MEDI-507*. DailyDrugNews.com (Daily Essentials) 1998, May 19.

MONOGRAPH – Sorbera, L.A. et al. *Siplizumab*. Drugs Fut 2002, 27(6): 0558.

MISCELLANEOUS DERMATOLOGIC DRUGS

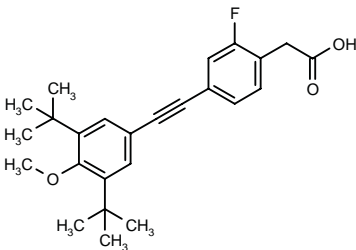
321187

2-[4-(3,5-Di-*tert*-butyl-4-methoxyphenylethynyl)phenyl]-acetic acid



C25 H30 O3; Mol wt: 378.5090

ACTION – Agent with the ability to inhibit retinoic acid-inducible cytochrome P-450 (P-450RAI), potentially useful for the treatment of a broad range of disorders, i.e., skin disorders such as keratoses, acne, psoriasis and atopic dermatitis, microbial infections, type 2 diabetes, cancer, ocular diseases such as proliferative vitreoretinopathy, retinal detachment and dry eye, dyslipidemia, post-angioplasty restenosis, human papillomavirus infections, inflammatory conditions such as pulmonary fibrosis, ileitis, colitis and Crohn’s disease, Alzheimer’s disease, Parkinson’s disease, stroke, immune disorders, transplant rejection and wound healing. Another specifically claimed compound is:



321188: C25 H29 F O3

SOURCE – Allergan.

REFERENCES

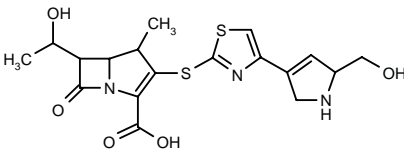
1. Vasudevan, J. et al. (Allergan, Inc.) *Cpds. having activity as inhibitors of cytochrome P450RAI*. US 6387951.

ANTIINFECTIVE THERAPY

ANTIBIOTICS

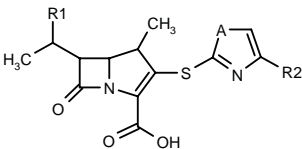
321453

6-(1-Hydroxyethyl)-2-[4-[5-(hydroxymethyl)-2,5-dihydro-1*H*-pyrrol-3-yl]thiazol-2-ylsulfanyl]-1-methyl-1-carba-2-penem-3-carboxylic acid

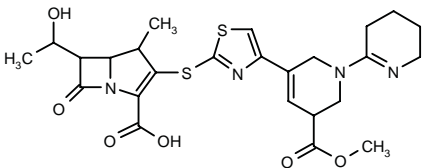


C18 H21 N3 O5 S2; Mol wt: 423.5119

ACTION – Carbapenem antibiotic, particularly useful for the treatment of infections caused by methicillin-resistant *Staphylococcus aureus* and methicillin-resistant coagulase-negative staphylococcal strains. Other exemplified β -lactams are:



Compound	R1	R2	A	Formula
321454	OH	2-(CH2OH)-1-(NH=CH)- -2,5-dihydro-1H-pyrrol-3-yl	S	C ₁₉ H ₂₂ N ₄ O ₅ S ₂
321456	OH	2-(CH2OH)-1,2,3,6-tetrahydro-4-Pyr	S	C ₁₉ H ₂₃ N ₃ O ₅ S ₂
321457	OH	1-(OHCH2CH2)-6-Me- -1,2,3,6-tetrahydro-4-Pyr	S	C ₂₁ H ₂₇ N ₃ O ₅ S ₂
321458	OH	6-(MeNHSO2NH)- -1,2,5,6-tetrahydro-3-Pyr	S	C ₁₉ H ₂₅ N ₅ O ₆ S ₃
321459	OH	2-Me-1-(MeNHCOCH2)- -1,2,3,6-tetrahydro-4-Pyr	S	C ₂₂ H ₂₈ N ₄ O ₅ S ₂
321460	OH	4-(CH2OH)-1-[MeNHC(=NH)]- -2,5-dihydro-1H-pyrrol-3-yl	S	C ₂₀ H ₂₅ N ₅ O ₅ S ₂
321463	Me	2-(CH2OH)-1,2,3,6-tetrahydro-4-Pyr	O	C ₂₀ H ₂₅ N ₃ O ₅ S



321461: C25 H30 N4 O6 S2

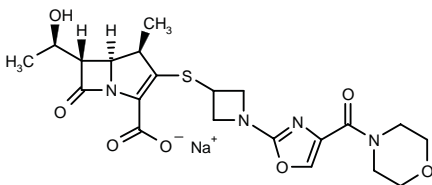
SOURCE – Sumitomo Pharmaceuticals.

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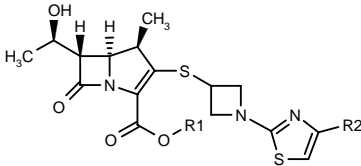
321745

(1*R*,5*S*,6*S*)-6-[1(*R*)-Hydroxyethyl]-1-methyl-2-[1-[4-(morpholin-4-ylcarbonyl)oxazol-2-yl]azetidin-3-ylsulfanyl]-1-carba-2-penem-3-carboxylic acid sodium salt



C21 H25 N4 Na O7 S; Mol wt: 500.5055

ACTION – Carbapenem antibiotic with stability to dehydropeptidase I and β-lactamases. Compound gave MIC values of 0.05, 0.20 and 0.39 μg/ml, respectively, against *Staphylococcus aureus* 209P, *Pneumococcus* 10664 and *Haemophilus influenzae* 9787 strains. It also demonstrated *in vivo* antibacterial activity against *Streptococcus pneumoniae* 9065 in mice, with an ED₅₀ value of 0.534 mg/kg s.c. Other exemplified 1-methyl-carbapenem derivatives are:



Compound	R1	R2	Formula
321746	Na	CONH2	C ₁₇ H ₁₉ N ₄ NaO ₅ S ₂
321749	Na	1-azetidiny-CO	C ₂₀ H ₂₃ N ₄ NaO ₅ S ₂
321750	H	3(S)-pyrrolidiny-NHCO	C ₂₁ H ₂₇ N ₅ O ₅ S ₂
321751	H	3(R)-pyrrolidiny-NHCO	C ₂₁ H ₂₇ N ₅ O ₅ S ₂
321752	H	3-azetidiny-NHCO	C ₂₀ H ₂₅ N ₅ O ₅ S ₂
321753	H	1-Piz-CO	C ₂₁ H ₂₇ N ₅ O ₅ S ₂
321754	H	CONHCH2CH2NH2	C ₁₉ H ₂₅ N ₅ O ₅ S ₂
321755	H	CH2NH2	C ₁₇ H ₂₂ N ₄ O ₄ S ₂

SOURCE – Sankyo.

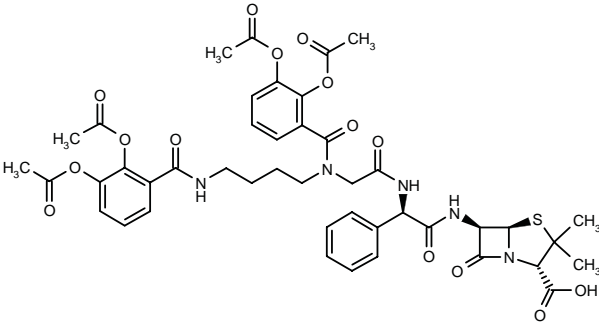
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HKI-9924154

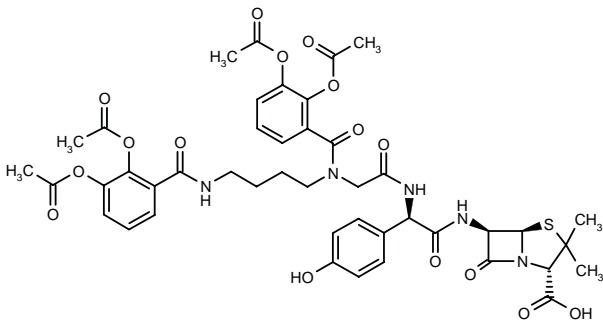
312947

(2*S*,5*R*,6*R*)-6-[2(*R*)-[2-[*N*-(2,3-Diacetoxybenzoyl)-*N*-[4-(2,3-diacetoxybenzamido)butyl]amino]acetamido]-2-phenylacetamido]-3,3-dimethyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylic acid



C44 H47 N5 O15 S; Mol wt: 917.9413

ACTION – Antibiotic, acylaminopenicillin siderophore conjugate with very strong antibacterial activity against Gram-negative bacteria including *Pseudomonas aeruginosa*, *Stenotrophomonas maltophilia*, *Escherichia coli*, *Klebsiella pneumoniae* and *Serratia marcescens* (MIC = 5 ng/ml or less); less activity was seen against *Staphylococcus aureus* (MIC = 5 μg/ml). The conjugate can use bacterial iron siderophore uptake routes to penetrate the bacterial outer membrane. Compound was also active in a model of murine septicemia and exhibited low acute toxicity. Another related compound is:



HKI-9924155 [312948]: C44 H47 N5 O16 S

SOURCES – Grünenthal; Hans Knöll Institute for Natural Products Research, Jena (DE).

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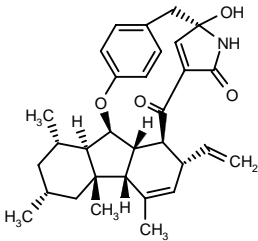
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PYRROCIDINE A

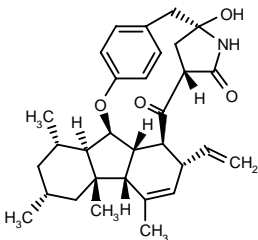
321056

(7*R**,11*aS**,12*R**,14*aR**,14*bS**,16*R**,18*S**,18*aR**,18*bS**,18*cS**)-7-Hydroxy-14,14*b*,16,18-tetramethyl-12-vinyl-6,7,8,9,11,11*a*,12,14*a*,14*b*,15,16,17,18,18*a*,18*b*,18*c*-hexadecahydro-2,5-etheno-7,10-methenofluoreno-[9,1-*bc*][1,8]oxazacyclotetradecine-9,11-dione



C31 H37 N O4; Mol wt: 487.6363

ACTION – Antibiotic produced by filamentous fungus LL-Cyan426 with strong activity against Gram-positive bacteria including *Streptococcus haemolyticus* (MIC = 0.25 µg/ml), *Enterococcus faecalis* (MIC = 0.5 µg/ml), as well as sensitive and resistant strains of *Staphylococcus aureus* (MIC = 0.254-2 µg/ml) and *Enterococcus faecium* (MIC = 0.5-1 µg/ml). Another related compound is:



Pyrrocidine B [321061]: C31 H39 N O4

SOURCE – Wyeth.

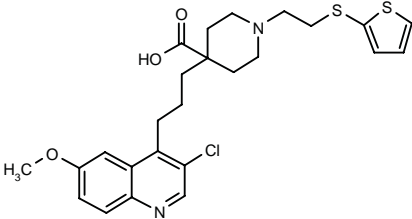
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1. He, H.Y. et al. *Pyrrocidines A and B, new antibiotics produced by a filamentous fungus.* Tetrahedron Lett 2002, 43(9): 1633.

ANTIBACTERIAL DRUGS

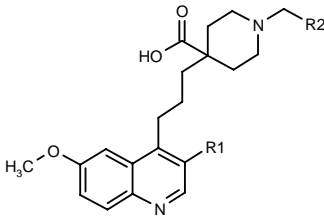
321933

4-[3-(3-Chloro-6-methoxyquinolin-4-yl)propyl]-1-[2-(thien-2-ylsulfanyl)ethyl]piperidine-4-carboxylic acid



C25 H29 Cl N2 O3 S2; Mol wt: 505.1001

ACTION – Antibacterial agent, a representative compound from a series of heterocyclylalkyl piperidine derivatives, wherein the following are also included:



Compound	R1	R2	Formula
321937	Cl	3,5-(F)2-PhOCH2	C ₂₇ H ₂₉ ClF ₂ N ₂ O ₄
321939	Cl	2-thiazolyl-SCH2	C ₂₄ H ₂₈ ClN ₃ O ₃ S ₂
321941	F	cyclopentyl-SCH2	C ₂₆ H ₃₅ FN ₂ O ₃ S
321942	F	CH=CHPh	C ₂₈ H ₃₁ FN ₂ O ₃

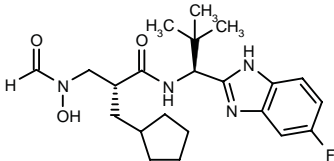
SOURCE – Aventis Pharma.

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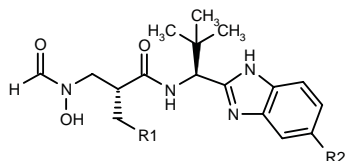
322139

3-Cyclopentyl-*N*-[1(*S*)-(5-fluoro-1*H*-benzimidazol-2-yl)-2,2-dimethylpropyl]-2(*R*)-(*N*-formyl-*N*-hydroxyamino-methyl)propionamide



C22 H31 F N4 O3; Mol wt: 418.5099

ACTION – Antibacterial and antiprotozoal agent that demonstrated *in vitro* activity against *Staphylococcus aureus* ATCC 29213 (MIC = 4 µg/ml) and *Streptococcus pneumoniae* ATCC 49619 (MIC = 2 µg/ml). Other exemplified hydroxamic acids are:



Compound	R1	R2	Formula
322140	cyclopentyl	Cl	C ₂₂ H ₃₁ ClN ₄ O ₃
322141	cyclopentyl	H	C ₂₂ H ₃₂ N ₄ O ₃
322142	Pr	H	C ₂₀ H ₃₀ N ₄ O ₃

SOURCE – British Biotech.

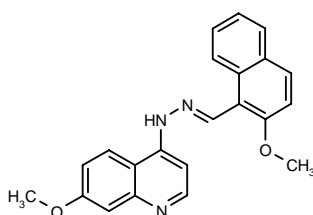
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ANTIMYCOBACTERIAL AGENTS

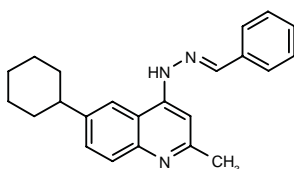
321945

2-Methoxy-1-naphthaldehyde (7-methoxyquinolin-4-yl)-hydrazone



C22 H19 N3 O2; Mol wt: 357.4111

ACTION – Antimycobacterial agent active against *Mycobacterium tuberculosis* (MIC = 6.25 µg/ml). It exhibited low cytotoxicity in Vero cells (CC₅₀ = 73 µg/ml) and was active in a tuberculosis-infected macrophage assay where it strongly reduced residual minimal mycobacterial growth (EC₉₀ = 0.65 µg/ml) after 7 days of exposure. Potentially useful for the treatment of tuberculosis. Another related compound is:



321946: C23 H25 N3

SOURCE – Università degli Studi di Siena, Siena (IT).

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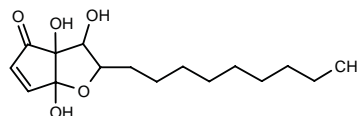
1. Savini, L. et al. *Synthesis and anti-tubercular evaluation of 4-quinolylhydrazones*. Bioorg Med Chem 2002, 10(7): 2193.

ANTIFUNGAL AGENTS

F-15784

321143

3,3a,6a-Trihydroxy-2-nonyl-3,3a,4,6a-tetrahydro-2H-cyclopenta[b]furan-4-one



C16 H26 O5; Mol wt: 298.3764

ACTION – Antifungal compound isolated from cultures of *Rigidoporus lineatus* SANK 10499 (FERM BP-7280), with *in vitro* activity against *Candida albicans* YU1200, *Aspergillus niger* SNAK22667 and *Trichophyton mentagrophytes* SANK11868.

SOURCE – Sankyo.

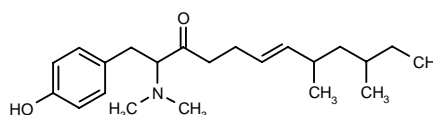
REFERENCES

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Q-73453A

322326

2-(Dimethylamino)-1-(4-hydroxyphenyl)-8,10-dimethyl-6-dodecen-3-one



C22 H35 N O2; Mol wt: 345.5235

ACTION – Antifungal compound isolated from cultures of *Pseudallescheria ellipsoidea* CBS 128.78 strain. This compound demonstrated *in vitro* activity against *Candida albicans* ATCC10231, with an MIC of 0.16 mg/ml.

SOURCE – Yamanouchi.

REFERENCES

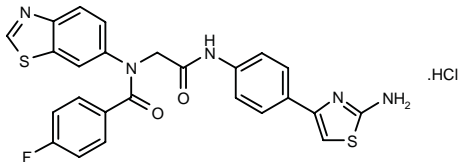
1. Tanaka, K. et al. (Yamanouchi Pharmaceutical Co., Ltd.) *Novel antifungal cpds. and their preparation method*. JP 2002155036.

ANTIVIRAL DRUGS

321333

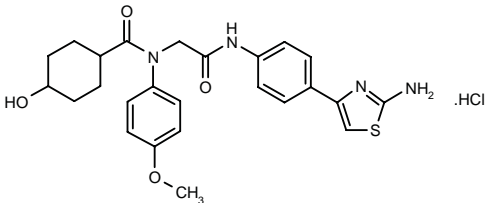
N-[*N*-[4-(2-Aminothiazol-4-yl)phenyl]carbamoylmethyl]-*N*-(benzothiazol-6-yl)-4-fluorobenzamide hydrochloride

*N*¹-[4-(2-Aminothiazol-4-yl)phenyl]-*N*²-(benzothiazol-6-yl)-*N*²-(4-fluorobenzoyl)glycinamide hydrochloride



C25 H18 F N5 O2 S2 . HCl; Mol wt: 540.0411

ACTION – Antiviral agent for use in the treatment of infections caused by herpesvirus including varicella-zoster virus (VZV), herpes labialis, herpes encephalitis caused by herpes simplex virus type 1 (HSV-1) and genital herpes caused by HSV-2. In a mouse model of HSV-1 dermal infection, oral administration at 25 mg/kg/day for 5 days resulted in almost complete inhibition of dermal lesions and prolongation of survival time. No deaths were observed during the treatment. Another exemplified amide derivative is:



321334: C25 H28 N4 O4 S . H Cl

SOURCES – Rational Drug Design Laboratories, Fukushima (JP); Yamanouchi.

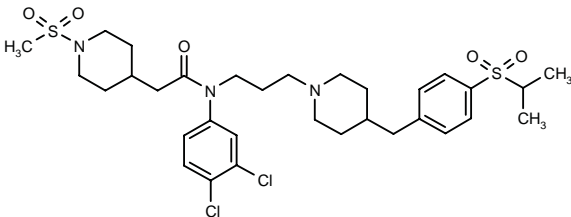
REFERENCES

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AIDS MEDICINES

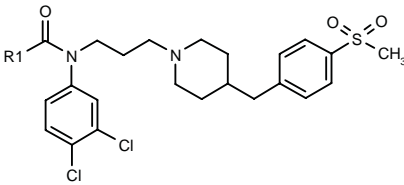
321338

N-(3,4-Dichlorophenyl)-*N*-[3-[4-[4-(isopropylsulfonyl)-benzyl]piperidin-1-yl]propyl]-2-[1-(methylsulfonyl)-piperidin-4-yl]acetamide



C32 H45 Cl2 N3 O5 S2; Mol wt: 686.7615

ACTION– Chemokine CCR5 receptor antagonist reported to inhibit [¹²⁵I]-RANTES binding to CCR5 receptors expressed in CHO cells by 99% at 1.0 μM. Potentially useful for the treatment of HIV infection. Other exemplified piperidine derivatives are:



Compound	R1	Formula
321339	1-(MeSO2)-4-Pip-CH2	C ₃₀ H ₄₁ Cl ₂ N ₃ O ₅ S ₂
321340	1-Ac-4-Pip-CH2CH2	C ₃₂ H ₄₃ Cl ₂ N ₃ O ₄ S
321341	1-(MeSO2)-4-OH-4-Pip	C ₂₉ H ₃₉ Cl ₂ N ₃ O ₆ S ₂

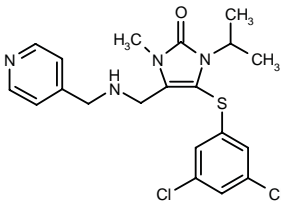
SOURCE – Takeda.

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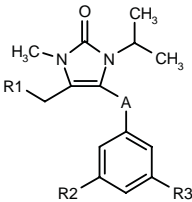
321662

4-(3,5-Dichlorophenylsulfonyl)-3-isopropyl-1-methyl-5-(pyridin-4-ylmethylaminomethyl)-2,3-dihydro-1*H*-imidazol-2-one



C20 H22 Cl2 N4 O S; Mol wt: 437.3928

ACTION – HIV reverse transcriptase inhibitor (IC₅₀ = 90 nM), potentially useful for the treatment of HIV infection. This compound was shown to protect HIV-infected lymphoblastoid MT-4 cells from death with an IC₅₀ of 7 nM. Other exemplified imidazolone derivatives are:



Compound	R1	R2=R3	A	Formula
321663	4-Pyr-CH2O	Cl	S	C ₂₀ H ₂₁ Cl ₂ N ₃ O ₂ S
321664	4-Pyr-CH2NH	H	S	C ₂₀ H ₂₄ N ₄ OS
321665	NHCH2Ph	H	S	C ₂₁ H ₂₅ N ₃ OS
321666	4-Pyr-CH2NH	Cl	O	C ₂₀ H ₂₂ Cl ₂ N ₄ O ₂
321667	4-Pyr	Cl	S	C ₁₉ H ₁₉ Cl ₂ N ₃ OS
321668	4-Pyr-O	Cl	S	C ₁₉ H ₁₉ Cl ₂ N ₃ O ₂ S
321669	3-Pyr-CH2O	Cl	S	C ₂₀ H ₂₁ Cl ₂ N ₃ O ₂ S

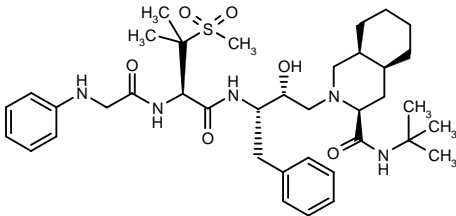
SOURCE – Roche.

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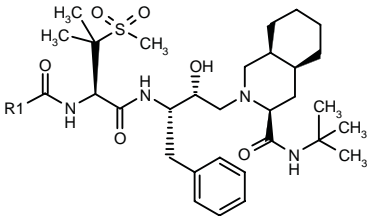
321671

(3*S*,4*aS*,8*aS*)-*N-tert*-Butyl-2-[2(*R*)-hydroxy-4-phenyl-3(*S*)-[*N*-phenylglycyl-3-(methylsulfonyl)-*L*-valylamino]-butyl]perhydroisoquinoline-3-carboxamide



C38 H57 N5 O6 S; Mol wt: 711.9633

ACTION – HIV protease inhibitor (IC₅₀ = 0.5 nM), potentially useful for the treatment of HIV infection. This compound was shown to protect HIV-infected lymphoblastoid MT-4 cells from death with an IC₅₀ of 8 nM. Other exemplified compounds are:



Compound	R1	Formula
321672	3-Pyr-OCH2	C ₃₇ H ₅₈ N ₅ O ₇ S
321673	2-Pyr-OCH2	C ₃₇ H ₅₈ N ₅ O ₇ S
321674	3-pyridazinyl-OCH2	C ₃₆ H ₅₄ N ₆ O ₇ S
321675	NHCH2Ph	C ₃₈ H ₅₇ N ₅ O ₆ S
321676	3-Pyr-CH2N(Me)	C ₃₈ H ₅₈ N ₆ O ₆ S

SOURCE – Roche.

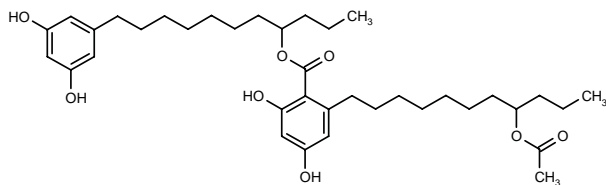
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INTEGRACIN A

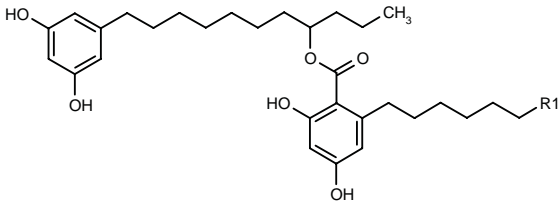
321046

2-(8-Acetoxyundecyl)-4,6-dihydroxybenzoic acid 8-(3,5-dihydroxyphenyl)-1-propyloctyl ester



C37 H56 O8; Mol wt: 628.8414

ACTION – Anti HIV-1 agent, a natural product extracted from the fungus *Cytonaema* sp. with HIV-1 integrase-inhibitory activity (IC₅₀ = 3.2 and 32 μM in HIV-1 integrase coupled and strand transfer assays, respectively). Other related compounds are:



Compound	R1	Formula
Integracin B [321047]	CH2CH(OH)Pr	C ₃₅ H ₅₄ O ₇
Integracin C [321048]	CH=CHPr	C ₃₅ H ₅₂ O ₆

SOURCES – Merck & Co.; Merck Sharp & Dohme.

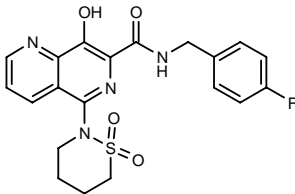
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L-870810*

320387

5-(1,1-Dioxoperhydro-1,2-thiazin-2-yl)-*N*-(4-fluorobenzyl)-8-hydroxy-1,6-naphthyridine-7-carboxamide



C20 H19 F N4 O4 S; Mol wt: 430.4581

ACTION – HIV-1 integrase inhibitor (IC₅₀ = 10 nM) with potent antiviral activity against various HIV-1 strains (IC₉₅ = 15-104 nM) including multidrug-resistant clinical isolates (IC₅₀ = 4 nM). Compound exhibited a favorable pharmacokinetic profile in animals, with an oral bioavailability of 24% in dogs and 41% in rats and a terminal elimination half-life of 14 h in rats after a dose of 1 mg/kg i.v. Phase I clinical studies are currently under way.

SOURCE – Merck & Co.

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- Young, S. et al. *L-870,810: A potent antiviral HIV integrase inhibitor with potential clinical utility*. 14th Int AIDS Conf (July 7-12, Barcelona) 2002, Abst LBPEA9007.

*Identified compound **320387** Drug Data Rep 2002, 024(07): 0634.

SPD-756*

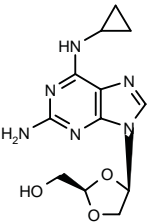
292083

(-)-(2*R*,4*R*)-4-[2-Amino-6-(cyclopropylamino)-9*H*-purin-9-yl]-1,3-dioxolane-2-methanol

(-)-(2*R*,4*R*)-4-[2-Amino-6-(cyclopropylamino)-9*H*-purin-9-yl]-2-(hydroxymethyl)-1,3-dioxolane

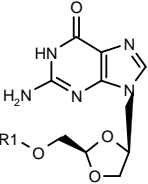
N⁶-Cyclopropyl-9-[2(*R*)-(hydroxymethyl)-1,3-dioxolan-4(*R*)-yl]purine-2,6-diamine

BCH-13520



C12 H16 N6 O3; Mol wt: 292.2974

ACTION – Nucleoside reverse transcriptase inhibitor, a prodrug of **SPD-761** with potent anti-HIV-1 activity (IC₅₀ = 0.14-0.63 μM) that retains high activity against clinical isolates and strains resistant to zidovudine and/or lamivudine without showing significant cytotoxicity in primary cells and established cell lines (CC₅₀ > 308 μM). Low-level resistance to the drug slowly emerges *in vitro* and is associated with V75I, K65R, M16I, K103R and G196R mutations. Experiments in human and mouse liver microsomes showed that com-pound was metabolized, mainly by cytochrome P-450 CYP1A2 enzymes, to 4 metabolites, the major active metabolite being **SPD-761 triphosphate** (SPD-761-TP), with potent HIV reverse transcriptase-inhibitory activity (K_i = 13 nM). Pharmacokinetic studies in healthy men showed that compound (100, 200, 400, 800 or 1200 mg) was well absorbed (C_{max} = 1261-12,348 ng/ml; t_{max} = 0.75-1.25 h), with plasma levels greatly exceeding the *in vitro* IC₅₀ against wild-type HIV (64 ng/ml). The majority of the dose was cleared renally, but nonrenal clearance was also involved. SPD-756 is currently in phase I trials.



Compound	R1	Formula
SPD-761 [204762]** DXG; (-)-BCH-187	H	C ₉ H ₁₁ N ₅ O ₄
SPD-761-TP [307361] DXG-TP	PO(OH)OPO(OH)OPO3H2	C ₉ H ₁₄ N ₅ O ₁₃ P ₃

SOURCE – Shire BioChem.

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2. Cimpoia, A. and Wang, Y.-F. (Shire BioChem Inc.) *Stereoselective synthesis of nucleoside analogues*. WO 0158894.

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29. *Shire summarizes quarter's R&D highlights.* DailyDrugNews.com (Daily Essentials) 2002, Dec 30.

30. *Therapeutic pipeline update provided by BioChem Pharma.* DailyDrugNews.com (Daily Essentials) 2001, May 15.

31. *Therapeutic products in development.* BioChem Pharma Web Site 2000, Nov 1.

*Identified compound **292083** Drug Data Rep 2000, 022(11): 1017.

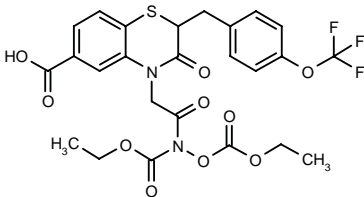
See (–)-BCH-571** Drug Data Rep 1994, 016(05): 0489.

TREATMENT OF MUSCULOSKELETAL AND CONNECTIVE TISSUE DISEASES

ANTIARTHRITIC DRUGS

321155

4-[*N*-(Ethoxycarbonyl)-*N*-(ethoxycarbonyloxy)carbamoylmethyl]-3-oxo-2-[4-(trifluoromethoxy)benzyl]-3,4-dihydro-2*H*-1,4-benzothiazine-6-carboxylic acid



C25 H23 F3 N2 O10 S; Mol wt: 600.5207

ACTION – A representative compound from a series of 4-(carbamoylmethyl)-1,4-benzothiazin-3-one derivatives that are orally available prodrugs of matrix metalloproteinase (MMP) inhibitors. This compound demonstrated good oral absorption following administration to rats at a dose of 30 mg/kg. It was transformed *in vivo* to the corresponding hydroxamic acid compound, which inhibited MMP-1 (interstitial collagenase), MMP-2 (gelatinase A), MMP-3 (stromelysin 1), MMP-9 (gelatinase B) and MMP-13 (collagenase 3) with respective IC₅₀ values of 42, 34, 62, 180 and 14 nM. Potentially useful for the treatment of osteoarthritis, rheumatoid arthritis, cancer and gingivitis.

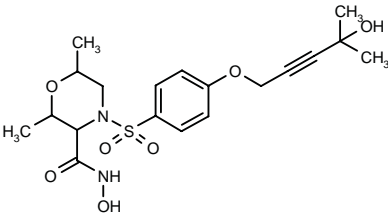
SOURCE – Sumitomo Pharmaceuticals.

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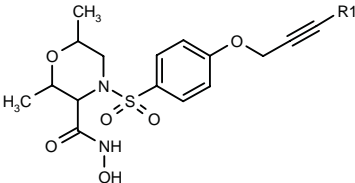
321159

4-[4-(4-Hydroxy-4-methyl-2-pentynyloxy)phenylsulfonyl]-2,6-dimethylmorpholine-3-carbohydroxamic acid



C19 H26 N2 O7 S; Mol wt: 426.4874

ACTION – An inhibitor of matrix metalloproteinases (MMPs) and reprotolysins (also known as ADAMs), potentially useful for the treatment of arthritis, inflammatory bowel disease, Crohn's disease, emphysema, acute respiratory distress syndrome, asthma, chronic obstructive pulmonary disease, Alzheimer's disease, cachexia, allergy, cancer, tissue ulceration, restenosis, periodontal disease, osteoporosis, atherosclerosis, congestive heart failure, myocardial infarction, stroke, head and spinal cord trauma, autoimmune disorders, etc. Other specifically claimed alkyne-containing compounds are:



Compound	R1	Formula
321160	Et	C ₁₈ H ₂₄ N ₂ O ₆ S
321161	Me	C ₁₇ H ₂₂ N ₂ O ₆ S
321162	Ph	C ₂₂ H ₂₄ N ₂ O ₆ S

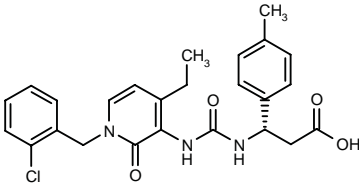
SOURCE – Pfizer.

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321259

3(*S*)-[3-[1-(2-Chlorobenzyl)-4-ethyl-2-oxo-1,2-dihydropyridin-3-yl]ureido]-3-(4-methylphenyl)propionic acid



C25 H26 Cl N3 O4; Mol wt: 467.9504

27. *BioChem Pharma reviews progress during the year.* DailyDrugNews.com (Daily Essentials) 2001, Jan 30.

28. *Shire highlights Q3 developments and updates product pipeline.* DailyDrugNews.com (Daily Essentials) 2001, Nov 20.

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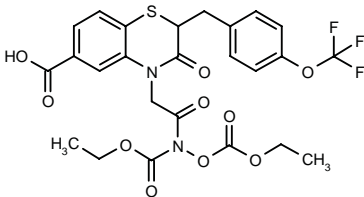
See (–)-BCH-571** Drug Data Rep 1994, 016(05): 0489.

TREATMENT OF MUSCULOSKELETAL AND CONNECTIVE TISSUE DISEASES

ANTIARTHRITIC DRUGS

321155

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C25 H23 F3 N2 O10 S; Mol wt: 600.5207

ACTION – A representative compound from a series of 4-(carbamoylmethyl)-1,4-benzothiazin-3-one derivatives that are orally available prodrugs of matrix metalloproteinase (MMP) inhibitors. This compound demonstrated good oral absorption following administration to rats at a dose of 30 mg/kg. It was transformed *in vivo* to the corresponding hydroxamic acid compound, which inhibited MMP-1 (interstitial collagenase), MMP-2 (gelatinase A), MMP-3 (stromelysin 1), MMP-9 (gelatinase B) and MMP-13 (collagenase 3) with respective IC₅₀ values of 42, 34, 62, 180 and 14 nM. Potentially useful for the treatment of osteoarthritis, rheumatoid arthritis, cancer and gingivitis.

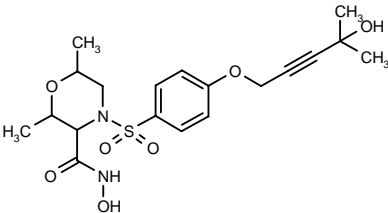
SOURCE – Sumitomo Pharmaceuticals.

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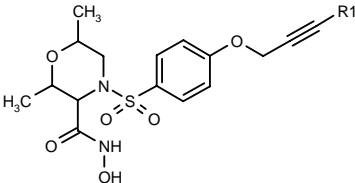
321159

4-[4-(4-Hydroxy-4-methyl-2-pentynyloxy)phenylsulfonyl]-2,6-dimethylmorpholine-3-carbohydroxamic acid



C19 H26 N2 O7 S; Mol wt: 426.4874

ACTION – An inhibitor of matrix metalloproteinases (MMPs) and reprotolysins (also known as ADAMs), potentially useful for the treatment of arthritis, inflammatory bowel disease, Crohn's disease, emphysema, acute respiratory distress syndrome, asthma, chronic obstructive pulmonary disease, Alzheimer's disease, cachexia, allergy, cancer, tissue ulceration, restenosis, periodontal disease, osteoporosis, atherosclerosis, congestive heart failure, myocardial infarction, stroke, head and spinal cord trauma, autoimmune disorders, etc. Other specifically claimed alkyne-containing compounds are:



Compound	R1	Formula
321160	Et	C ₁₈ H ₂₄ N ₂ O ₆ S
321161	Me	C ₁₇ H ₂₂ N ₂ O ₆ S
321162	Ph	C ₂₂ H ₂₄ N ₂ O ₆ S

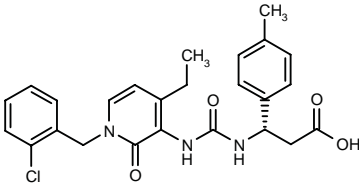
SOURCE – Pfizer.

REFERENCES

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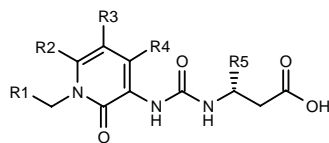
321259

3(*S*)-[3-[1-(2-Chlorobenzyl)-4-ethyl-2-oxo-1,2-dihydropyridin-3-yl]ureido]-3-(4-methylphenyl)propionic acid

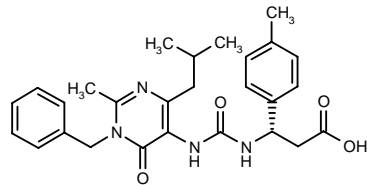


C25 H26 Cl N3 O4; Mol wt: 467.9504

ACTION – Agent with the ability to inhibit the binding of $\alpha_4\beta_1$ integrin to VCAM-1 and fibronectin, potentially useful for the treatment of atherosclerosis, rheumatoid arthritis, asthma, allergy, multiple sclerosis, lupus, inflammatory bowel disease, transplant rejection, contact hypersensitivity, type 1 diabetes and cancer. Other exemplified carboxylic acid derivatives are:



Compound	R1	R2	R3	R4	R5	Formula
321261	2-Cl-Ph	H	H	F	4-Me-Ph	C ₂₃ H ₂₁ ClFN ₃ O ₄
321267	2-thienyl	H	H	H	1,3-benzodioxol-5-yl	C ₂₁ H ₁₉ N ₃ O ₆ S
321268	cyclopentyl	H	H	H	1,3-benzodioxol-5-yl	C ₂₂ H ₂₅ N ₃ O ₆
321269	2-Cl-Ph	H	Me	OH	4-Me-Ph	C ₂₄ H ₂₄ ClN ₃ O ₅
321271	2-Cl-Ph	-(CH2)3-		OH	4-Me-Ph	C ₂₆ H ₂₆ ClN ₃ O ₅
321272	2-Cl-Ph	-(CH2)3-		OH	1,3-(Et)2-2-oxo-5-benzimidazolyl	C ₃₁ H ₃₃ ClN ₄ O ₆
321273	2-Cl-Ph	-(CH2)3-		OH	3-i-PrO-4-Cl-Ph	C ₂₈ H ₂₉ Cl ₂ N ₃ O ₆



321265: C27 H32 N4 O4

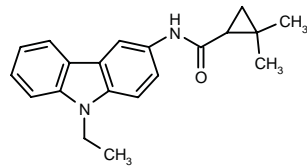
SOURCE – Texas Biotechnology.

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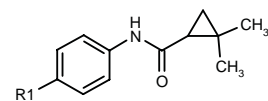
321519

N-(9-Ethyl-9*H*-carbazol-3-yl)-2,2-dimethylcyclopropane-carboxamide



C20 H22 N2 O; Mol wt: 306.4068

ACTION – Agent with the ability to inhibit the activation of NF- κ B, as demonstrated by inhibition of IL-1 β -stimulated NF- κ B activity in human umbilical vein endothelial cells (HUVEC; IC₅₀ = 2 μ g/ml). Compound is also reported to inhibit the production of inflammatory cytokines, matrix metalloproteinases and inflammatory cell adhesion factors, and is claimed for use in the treatment of inflammation, rheumatism, cancer metastasis, viral infections and arteriosclerosis, and also as an immunosuppressant. Other exemplified cyclopropanecarboxamide derivatives are:



Compound	R1	Formula
321520	CH2Ph	C ₁₉ H ₂₁ NO
321521	Me	C ₁₃ H ₁₇ NO
321523	4-Cl-PhO	C ₁₈ H ₁₈ ClNO ₂
321525	NHPh	C ₁₈ H ₂₀ N ₂ O

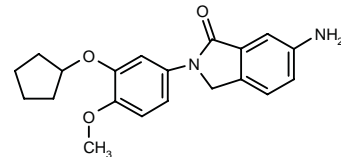
SOURCE – Ajinomoto.

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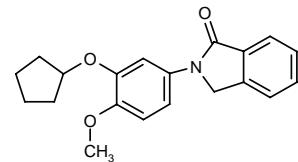
321587^{1,3}

6-Amino-2-[3-(cyclopentyloxy)-4-methoxyphenyl]iso-indolin-1-one



C20 H22 N2 O3; Mol wt: 338.4048

ACTION – TNF- α production inhibitor, a derivative of **DWP-205190** with improved activity in lipopolysaccharide (LPS)-stimulated RAW264.7 macrophages (IC₅₀ = 47 and 140 nM, respectively), potentially useful for the treatment of rheumatoid arthritis, Crohns disease, systemic lupus erythematosus, multiple sclerosis, asthma and AIDS.



DWP-205190 [321588]¹⁻⁴: C20 H21 N O3

SOURCE – Daewoong.

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1. Baik, K.-U. et al. (Daewoong Pharmaceutical Co., Ltd.) *Novel 3,4-dialkoxyphenyl derivs. and the use thereof.* WO 9842666.

2. Park, J.S. et al. *Novel 2-[3-(cyclopentyloxy)-4-methoxyphenyl]-1-isoindolinone derivatives. Part I: Synthesis and SAR studies for the inhibition of TNF- α production.* Arch Pharmacol Res 2001, 24(5): 367.

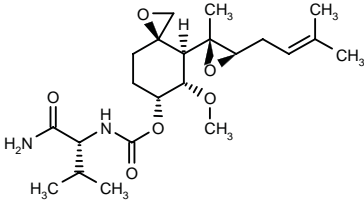
3. Park, J.S. et al. *Synthesis and SAR studies for the inhibition of TNF- α production. Part 2. 2-[3-(Cyclopentyloxy)-4-methoxyphenyl]-substituted-1-isoindolinone derivatives.* Arch Pharmacol Res 2002, 25(2): 137.

4. Park, J.J. et al. *Synthesis and structure activity relationships of novel compounds for the inhibition of TNF- α production.* Arch Pharmacol Res 2000, 23(4): 332.

321623

*N*²-[(3*R*,4*S*,5*S*,6*R*)-5-Methoxy-4-[2(*R*)-methyl-3(*R*)-(3-methyl-2-butenyl)oxiran-2-yl]-1-oxaspiro[2.5]oct-6-yloxy-carbonyl]-D-valinamide

6-*O*-[*N*-[1(*R*)-Carbamoyl-2-methylpropyl]carbamoyl]-fumagillol



C22 H36 N2 O6; Mol wt: 424.5344

ACTION – A representative compound from a series of amino acid-containing derivatives of the methionine aminopeptidase type 2 (MetAP2) inhibitor fumagillin. Compound inhibited the growth of human umbilical vein endothelial cells (HUVEC) and bovine aortic endothelial cells (BAEC) with IC₅₀ values of 93 and 46 pM, respectively. It was shown to be stable in human plasma (t_{1/2} > 500 min), and had a half-life of 12 min in rat liver microsomes (not affected by the presence of epoxide hydrolase inhibitors). It demonstrated a protective effect in a rat model of collagen-induced arthritis following either i.v. (15 and 30 mg/kg) or oral administration (100 mg/kg). Compound also exhibited antitumor activity against a wide variety of cancer cell lines. Potentially useful for the treatment of rheumatoid arthritis and cancer.

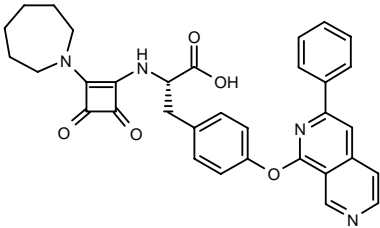
SOURCE – Praecis.

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1. Olson. G.L. et al. (Praecis Pharmaceuticals Inc.) *Therapeutic agents and methods of use thereof for the modulation of angiogenesis*. WO 0242295.

321625

N-[3,4-Dioxo-2-(perhydroazepin-1-yl)-1-cyclobuten-1-yl]-4-*O*-(3-phenyl-2,7-naphthyridin-1-yl)-L-tyrosine



C33 H30 N4 O5; Mol wt: 562.6230

ACTION – A potent and selective inhibitor of α₄ integrins, particularly α₄β₁ and/or α₄β₇ integrins. Potentially useful for the treatment of rheumatoid arthritis, vasculitis, polydermatomyositis, psoriasis, dermatitis, multiple sclerosis, transplant rejection, diabetes, asthma and inflammatory bowel disease.

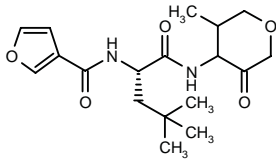
SOURCE – Celltech Group.

REFERENCES

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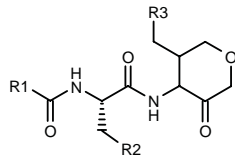
321710

*N*²-(Furan-3-ylcarbonyl)-4-methyl-*N*¹-(3-methyl-5-oxotetrahydropyran-4-yl)-L-leucinamide



C18 H26 N2 O5; Mol wt: 350.4124

ACTION – A selective inhibitor of cathepsin S, potentially useful for the treatment of autoimmune diseases, allergies, multiple sclerosis and rheumatoid arthritis, as well as other cathepsin S-mediated conditions. Other specifically claimed compounds are:



Compound	R1	R2	R3	Formula
321711	Ph	cyclohexyl	H	C ₂₂ H ₃₀ N ₂ O ₄
321712	Ph	cyclopentyl	H	C ₂₁ H ₂₈ N ₂ O ₄
321713	Ph	t-Bu	Me	C ₂₁ H ₃₀ N ₂ O ₄
321714	3-furyl	cyclopentyl	Me	C ₂₁ H ₃₀ N ₂ O ₅
321715	3-furyl	cyclohexyl	Et	C ₂₂ H ₃₂ N ₂ O ₅
321716	4-OH-3-Me-Ph	t-Bu	Et	C ₂₃ H ₃₄ N ₂ O ₅
321717	3-furyl	cyclopentyl	Et	C ₂₁ H ₃₀ N ₂ O ₅
321718	4-OH-3-Me-Ph	cyclopentyl	Et	C ₂₄ H ₃₄ N ₂ O ₅

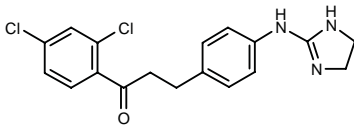
SOURCES – Genzyme General; Medivir.

REFERENCES

1. Quibell, M. et al. (Genzyme Corp.;Medivir UK Ltd.) *Cysteine protease inhibitors*. WO 0240462.

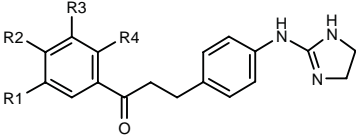
321887

1-(2,4-Dichlorophenyl)-3-[4-(4,5-dihydro-1*H*-imidazol-2-ylamino)phenyl]propan-1-one



C18 H17 Cl2 N3 O; Mol wt: 362.2583

ACTION – Prostaglandin I₂ (IP) receptor antagonist with a pK_i of 9.55 using human platelet IP receptors. Potentially useful for the treatment of pain, inflammation, urinary tract disorders, allergic respiratory diseases such as asthma, edema formation and hypotensive vascular conditions. Other exemplified compounds are:



Compound	R1	R2	R3	R4	Formula
321889	H	F	H	H	C ₁₈ H ₁₈ FN ₃ O
321890	H	4-(2-furyl-CO)-1-Piz	H	H	C ₂₇ H ₂₉ N ₅ O ₃
321892	H	i-PrO	H	H	C ₂₁ H ₂₅ N ₃ O ₂
321893	H	Cl	H	H	C ₁₈ H ₁₈ ClN ₃ O
321894	H	OMe	H	F	C ₁₉ H ₂₀ FN ₃ O ₂
321895	H	H	H	F	C ₁₈ H ₁₈ FN ₃ O
321896	F	Cl	H	Cl	C ₁₈ H ₁₆ Cl ₂ FN ₃ O
321897	F	H	H	H	C ₁₈ H ₁₈ FN ₃ O
321898	-CH=CHC(Me)=CH-		H	H	C ₂₃ H ₂₃ N ₃ O ₂
321899	F	H	F	H	C ₁₈ H ₁₇ F ₂ N ₃ O

SOURCE – Roche.

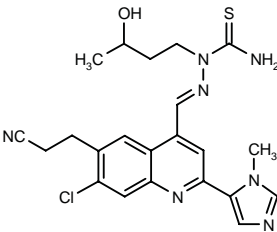
REFERENCES

1. Jahangir, A. (F. Hoffmann-La Roche AG) *Substd. 2-phenylaminoimidazoline phenyl ketone derivs. as IP antagonists.* WO 0240453.

322220

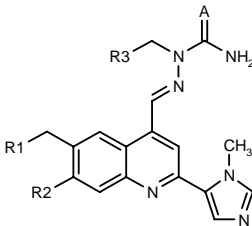
3-[7-Chloro-4-[2-(3-hydroxybutyl)thiosemicarbazono-methyl]-2-(1-methyl-1*H*-imidazol-5-yl)quinolin-6-yl]-propionitrile

7-Chloro-6-(2-cyanoethyl)-2-(1-methyl-1*H*-imidazol-5-yl)quinoline-4-carbaldehyde 2-(3-hydroxybutyl)thiosemi-carbazone



C22 H24 Cl N7 O S; Mol wt: 469.9986

ACTION – Modulator of IκB kinases (IKK) considered to have potential in the treatment of inflammatory and allergic disorders, autoimmune diseases, transplant rejection, cancer and metabolic disorders such as obesity, among other conditions mediated by activation of NF-κB. Other exemplified compounds are:



Compound	R1	R2	R3	A	Formula
322221	CH2CN	Cl	CH2C(Me)2OH	O	C ₂₃ H ₂₆ ClN ₇ O ₂
322222	CH2CN	Me	CH(OH)Me	O	C ₂₂ H ₂₅ N ₇ O ₂
322223	CH2CN	Cl	CH2C(Me)2OH	S	C ₂₃ H ₂₆ ClN ₇ OS
322224	CH2SO2Me	Me	CH2N(Et)2	S	C ₂₅ H ₃₅ N ₇ O ₂ S ₂
322225	CH2CN	Me	CH2CH(OH)Me	S	C ₂₃ H ₂₇ N ₇ OS
322226	CH2CN	Cl	1-Me-2-pyrrolidiny	S	C ₂₄ H ₂₇ ClN ₈ S
322227	4-THP	Me	CH2N(Me)2	S	C ₂₆ H ₃₅ N ₇ OS
322228	CH2CH2OMe	Me	CH2N(Et)2	S	C ₂₆ H ₃₇ N ₇ OS

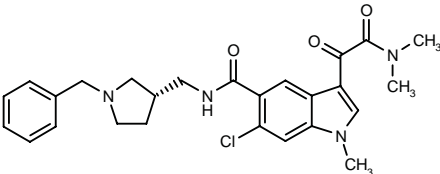
SOURCES – Roche; Tularik.

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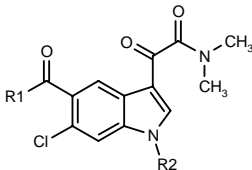
322339

N-[1-Benzylpyrrolidin-3(*S*)-ylmethyl]-6-chloro-3-[2-(di-methylamino)oxaly]-1-methyl-1*H*-indole-5-carboxamide



C26 H29 Cl N4 O3; Mol wt: 480.9931

ACTION – Inhibitor of p38α kinase with potential utility in the treatment of inflammatory disorders such as multiple sclerosis, arthritis, sepsis, asthma, adult respiratory distress syndrome, stroke, reperfusion injury, CNS injury, psoriasis, restenosis, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcosis, bone resorption, transplant rejection, Crohn’s disease, ulcerative colitis, Alzheimer’s disease and fever. Other specifically claimed compounds are:



Compound	R1	R2	Formula
322340	1-(PhCH2)-3(R)-pyrrolidiny-CH2NH	Me	C ₂₆ H ₂₉ ClN ₄ O ₃
322342	cis-5-(4-F-PhCH2)-3a,6a-(Me)2-perhydropyrrolo[3,4-c]pyrrol-2-yl	Me	C ₂₉ H ₃₂ ClFN ₄ O ₃
322343	1-(4-F-PhCH2)-4-Pip	Me	C ₂₆ H ₂₇ ClFN ₃ O ₃
322344	(1R,2R)-2-[4-F-PhCH2N(Me)]-cyclohexyl-NH	H	C ₂₇ H ₃₀ ClFN ₄ O ₃

SOURCE – Scios.

REFERENCES

1. Dugar, S. et al. (Scios Inc.) *Indole-type inhibitors of p38 kinase*. WO 0244168.

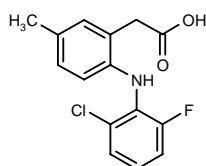
LUMIRACOXIB*

USAN

274891

2-[2-(2-Chloro-6-fluorophenylamino)-5-methylphenyl]-acetic acid

COX-189
Prexige™



C15 H13 Cl F N O2; Mol wt: 293.7237

ACTION – Selective cyclooxygenase type 2 (COX-2) inhibitor (IC₅₀ = 0.1 and 70 μM for COX-2 and COX-1 inhibition, respectively, in human whole blood) with 100- and 1,400-fold improved COX-2 selectivity compared to the NSAIDs diclofenac and naproxen, respectively. Results of phase I studies in healthy volunteers demonstrated that it was well tolerated after both single (up to 800 mg) and multiple (up to 600 mg over 9 days) oral doses, with dose-proportional exposure over the dose range relevant for clinical use. No gastrointestinal lesions and no changes in small bowel permeability were seen in healthy volunteers after 7 days of treatment with 200 mg b.i.d., in comparison with naproxen 500 mg b.i.d. An exploratory analysis of a multinational study in osteoarthritis patients showed that compound at 400 mg once daily is highly effective and comparable to diclofenac with respect to treatment response defined as a 20% reduction in osteoarthritis pain intensity. Compound is currently undergoing phase III evaluation for the treatment of arthritis and pain.

SOURCE – Novartis.

REFERENCES

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2. Bateman, S.D. et al. (Novartis AG;Novartis-Erfindungen VmbH) *Pharmaceutical compsns*. WO 0220090.
3. Fujimoto, R.A. et al. (Novartis AG) *Certain 5-alkyl-2-arylamino phenylacetic acids and derivs*. JP 2001514244, US 6291523, WO 9911605.
4. Atherton, C.T. et al. *COX-189, a new highly selective COX-2 inhibitor that lacks the ability of naproxen to enhance small bowel permeability*. Eur Leag Against Rheum Congr (June 12-15, Stockholm) 2002, Abst FRI0312.
5. Ebeling, T. *Driving growth*. Novartis R&D Invest Semin (Dec 6, Basel) 2000.
6. Hawkey, C. et al. *Reduced cumulative incidence of gastroduodenal ulcers with two doses of a new coxib, COX189 compared with standard therapeutic doses of ibuprofen in osteoarthritis patients*. Dig Dis Week (May 19-22, San Francisco) 2002, Abst M1732.
7. Hawkey, C.J. et al. *Improved upper gastrointestinal (UGI) safety and tolerability of a new coxib, COX189 compared with ibuprofen in osteoarthritis patients*. Eur Leag Against Rheum Congr (June 12-15, Stockholm) 2002, Abst THU0226.
8. Manning, D.C. et al. *Temporal aspects of COX189 efficacy in acute dental pain*. Clin Pharmacol Ther 2002, 71(2): Abst MPI-47.

9. Marshall, P.J. et al. *The in vitro and in vivo selectivity of COX189, a new and highly selective inhibitor of COX-2*. Eur Leag Against Rheum Congr (June 12-15, Stockholm) 2002, Abst SAT0013.

10. Moore, A. et al. *Responder rate of COX189 in osteoarthritis: A multi-national study*. Eur Leag Against Rheum Congr (June 12-15, Stockholm) 2002, Abst THU0265.

11. Reinhardt, J. *Innovation and productivity drive sustained growth*. Novartis R&D Invest Semin (Dec 6, Basel) 2000.

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13. Rordorf, C. et al. *Steady state pharmacokinetics, pharmacodynamics, safety and tolerability of COX189 in healthy subjects*. Eur Leag Against Rheum Congr (June 12-15, Stockholm) 2002, Abst AB0284.

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15. Scott, G. et al. *Dose escalation study to assess the safety, tolerability, pharmacokinetics and pharmacodynamics of COX189 in healthy subjects*. Eur Leag Against Rheum Congr (June 12-15, Stockholm) 2002, Abst FRI0300.

16. Scott, G. et al. *Pharmacokinetics and pharmacodynamics of COX189 in patients with knee or hip primary osteoarthritis*. Eur Leag Against Rheum Congr (June 12-15, Stockholm) 2002, Abst THU0233.

17. Schnitzer, T.J. et al. *Efficacy and safety of COX189 in osteoarthritis: A multi-national study*. 64th Annu Meet Am Coll Rheumatol (Oct 29-Nov2, Philadelphia) 2000, Abst 1616.

18. Novartis - *Accelerating growth*. 22nd Goldman Sachs Health Care Conf (June 11-14, Laguna Niguel) 2001.

19. Novartis launches *TARGET* trial of Prexige in arthritis. DailyDrugNews.com (Daily Essentials) 2002, May 22.

20. Novartis R&D day 1999: *Innovation drives future growth*. DailyDrugNews.com (Daily Essentials) 1999, Sept 24.

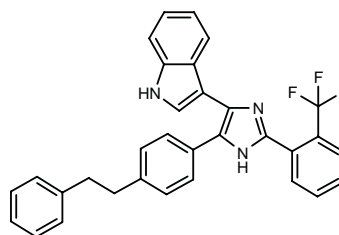
21. Novartis R&D day 2001: *Solid platform for sustained growth*. DailyDrugNews.com (Daily Essentials) 2001, Nov 7.

*Identified compound **274891** (see **274890**) Drug Data Rep 1999, 021(05): 0446.

SKA-1002

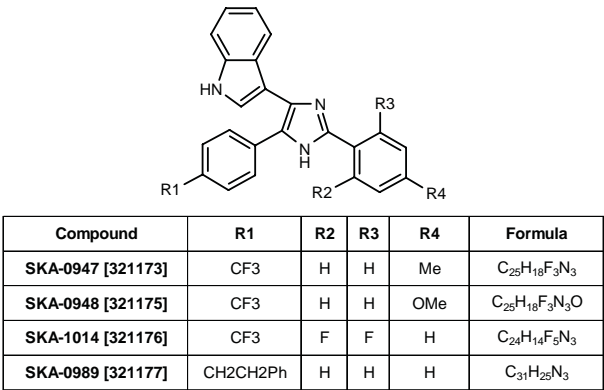
321171

3-[5-[4-(2-Phenylethyl)phenyl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl]-1H-indole



C32 H24 F3 N3; Mol wt: 507.5566

ACTION – Agent with the ability to inhibit the production of IL-6, potentially useful for the treatment of immune diseases such as rheumatism and cancers such as multiple myeloma. Compound inhibited the production of IL-6 in human synovial interstitial cells by 57% at a concentration of 12.5 μM. Other exemplified 4-(3-indolyl)imidazole derivatives are:



SOURCES – Sagami; Taisho.

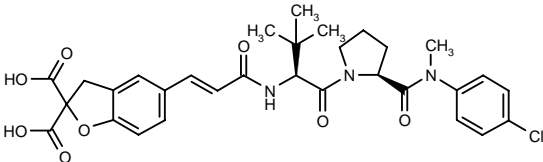
REFERENCES

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IMMUNOMODULATING DRUGS

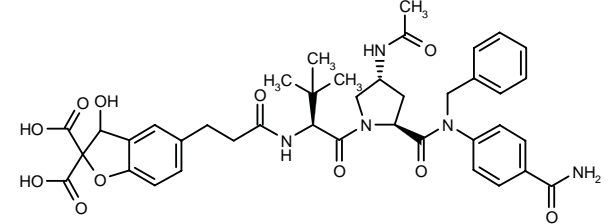
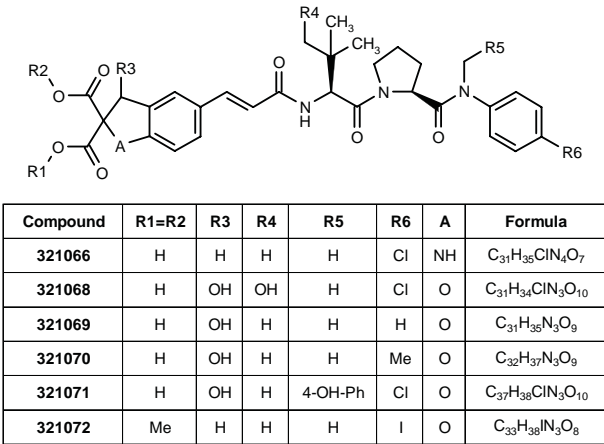
321064

N-[3-(2,2-Dicarboxy-2,3-dihydro-1-benzofuran-5-yl)-2-propenoyl]-3-methyl-L-valyl-N-(4-chlorophenyl)-N-methyl-L-prolinamide

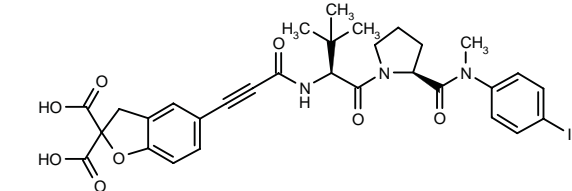


C31 H34 Cl N3 O8; Mol wt: 612.0756

ACTION – Agent with the ability to inhibit STAT6, potentially useful as an immunomodulating agent in the treatment of allergic rhinitis, asthma, atopic dermatitis, contact dermatitis, anaphylaxis, food or drug-induced allergy, conjunctivitis, uveitis, hypersensitivity reactions, alveolitis, psoriasis, Churg-Strauss syndrome, delayed-type hypersensitivity, urticaria, eczema, scleroderma and systemic lupus erythematosus. Other exemplified compounds are:



321065: C40 H45 N5 O11



321067: C31 H32 I N3 O8

SOURCE – Tularik.

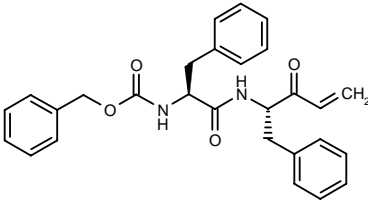
REFERENCES

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322045

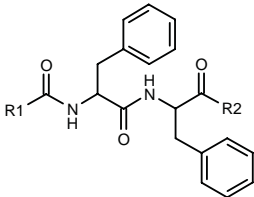
N¹-[1(S)-Benzyl-2-oxo-3-butenyl]-N²-(benzyloxycarbonyl)-L-phenylalaninamide

N-(Benzyloxycarbonyl)-L-phenylalanyl-L-phenylalanyl-ethylene

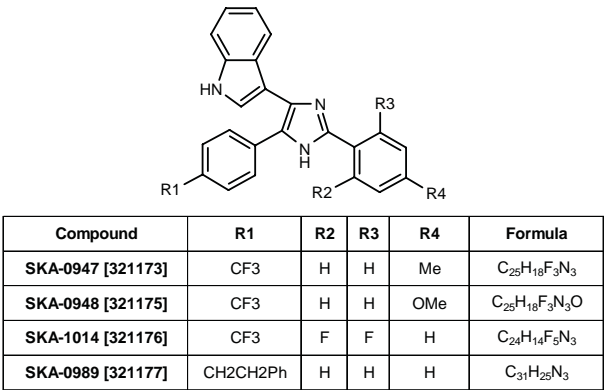


C28 H28 N2 O4; Mol wt: 456.5392

ACTION – Selective inhibitor of the immune-type proteasome induced by interferon gamma (IC₅₀ = 0.73 µg/ml), exhibiting selectivity over the constitutive-type proteasome (IC₅₀ > 30 µg/ml). Potentially useful as an immunosuppressant, antiinflammatory and antiallergic agent. Other exemplified compounds are:



Compound	R1	R2	Formula
322046	2,4-(Cl)2-Ph	vinyl	C ₂₇ H ₂₄ Cl ₂ N ₂ O ₃
322047	2-F-5-Me-Ph	vinyl	C ₂₈ H ₂₇ FN ₂ O ₃
322048	Ph	vinyl	C ₂₇ H ₂₆ N ₂ O ₃
322049	2-Naph	ethynyl	C ₃₁ H ₂₆ N ₂ O ₃
322050	OCH2Ph	ethynyl	C ₂₈ H ₂₆ N ₂ O ₄



SOURCES – Sagami; Taisho.

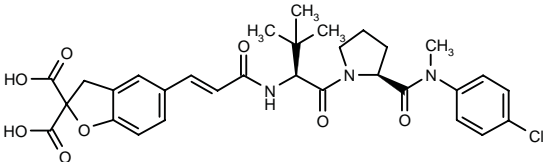
REFERENCES

1. Ohta, T. et al. (Taisho Pharmaceutical Co., Ltd.;Sagami Chemical Research Center) 4-(3-Indolyl)imidazole derivs. JP 2002114780.

IMMUNOMODULATING DRUGS

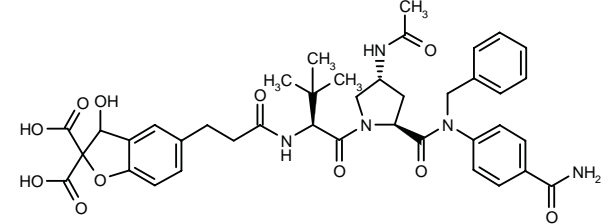
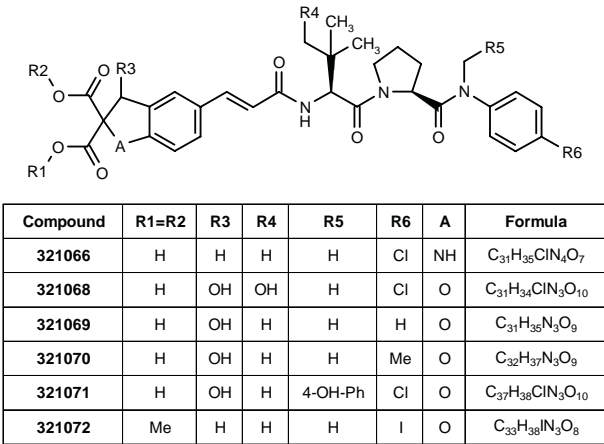
321064

N-[3-(2,2-Dicarboxy-2,3-dihydro-1-benzofuran-5-yl)-2-propenoyl]-3-methyl-L-valyl-N-(4-chlorophenyl)-N-methyl-L-prolinamide

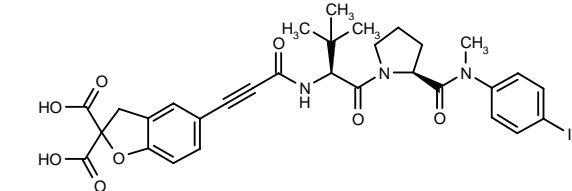


C31 H34 Cl N3 O8; Mol wt: 612.0756

ACTION – Agent with the ability to inhibit STAT6, potentially useful as an immunomodulating agent in the treatment of allergic rhinitis, asthma, atopic dermatitis, contact dermatitis, anaphylaxis, food or drug-induced allergy, conjunctivitis, uveitis, hypersensitivity reactions, alveolitis, psoriasis, Churg-Strauss syndrome, delayed-type hypersensitivity, urticaria, eczema, scleroderma and systemic lupus erythematosus. Other exemplified compounds are:



321065: C40 H45 N5 O11



321067: C31 H32 I N3 O8

SOURCE – Tularik.

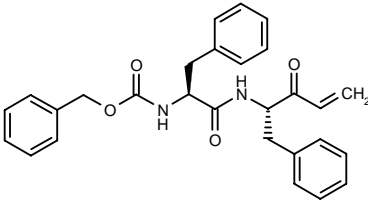
REFERENCES

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322045

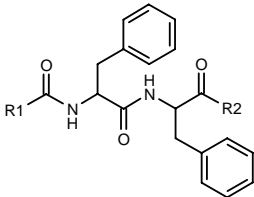
N¹-[1(S)-Benzyl-2-oxo-3-butenyl]-N²-(benzyloxycarbonyl)-L-phenylalaninamide

N-(Benzyloxycarbonyl)-L-phenylalanyl-L-phenylalanyl-ethylene



C28 H28 N2 O4; Mol wt: 456.5392

ACTION – Selective inhibitor of the immune-type proteasome induced by interferon gamma (IC₅₀ = 0.73 µg/ml), exhibiting selectivity over the constitutive-type proteasome (IC₅₀ > 30 µg/ml). Potentially useful as an immunosuppressant, antiinflammatory and antiallergic agent. Other exemplified compounds are:



Compound	R1	R2	Formula
322046	2,4-(Cl)2-Ph	vinyl	C ₂₇ H ₂₄ Cl ₂ N ₂ O ₃
322047	2-F-5-Me-Ph	vinyl	C ₂₈ H ₂₇ FN ₂ O ₃
322048	Ph	vinyl	C ₂₇ H ₂₆ N ₂ O ₃
322049	2-Naph	ethynyl	C ₃₁ H ₂₆ N ₂ O ₃
322050	OCH2Ph	ethynyl	C ₂₈ H ₂₆ N ₂ O ₄

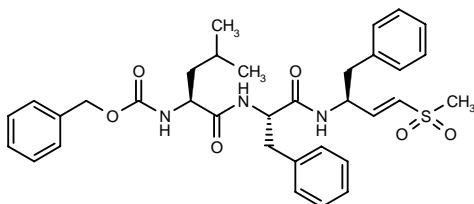
SOURCE – Kyorin.

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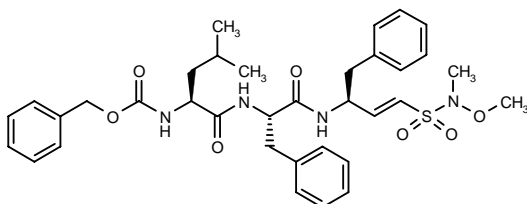
322106

N-(Benzyloxycarbonyl)-L-leucyl-*N*¹-[1(*S*)-benzyl-3-(methylsulfonyl)-2-propenyl]-L-phenylalaninamide



C34 H41 N3 O6 S; Mol wt: 619.7789

ACTION – Agent with proteasome-inhibitory activity (IC_{50} = 0.14 μ g/ml), also shown to inhibit NF- κ B activation (IC_{50} = 2.39 μ g/ml). In addition, it demonstrated activity in mouse models of delayed hypersensitivity reaction and graft-vs.-host reaction following administration at 50 mg/kg i.p. Potentially useful as an immunosuppressant, antiinflammatory and antiallergic agent, as well as in the treatment of immune and neurodegenerative diseases and cancer. Another exemplified compound is:



322107: C35 H44 N4 O7 S

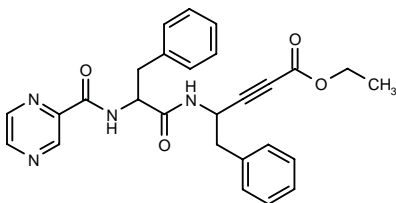
SOURCE – Kyorin.

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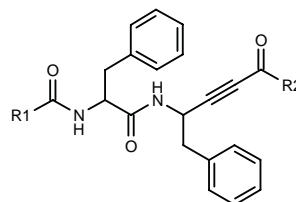
322109

5-Phenyl-4-[*N*-(pyrazin-2-ylcarbonyl)-DL-phenylalanyl-amino]-2-pentynoic acid ethyl ester



C27 H26 N4 O4; Mol wt: 470.5264

ACTION – Agent with proteasome-inhibitory activity (IC_{50} = 1.82 μ g/ml), also shown to inhibit NF- κ B activation (IC_{50} = 1.39 μ g/ml). Potentially useful as an immunosuppressant, antiinflammatory and antiallergic agent, as well as in the treatment of immune and neurodegenerative diseases and cancer. Other exemplified compounds are:



Compound	R1	R2	Isomer	Formula
322110	OCH2Ph	OEt		C ₃₀ H ₃₀ N ₂ O ₅
322111	CH=CHPh	OEt		C ₃₁ H ₃₀ N ₂ O ₄
322112	2-Naph	OEt		C ₃₃ H ₃₀ N ₂ O ₄
322113	OCH2Ph	Me	S,S	C ₂₉ H ₂₈ N ₂ O ₄

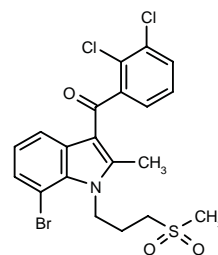
SOURCE – Kyorin.

REFERENCES

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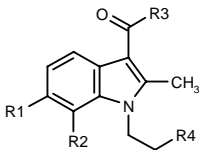
322196

1-[7-Bromo-2-methyl-1-[3-(methylsulfonyl)propyl]-1*H*-indol-3-yl]-1-(2,3-dichlorophenyl)methanone



C20 H18 Br Cl2 N O3 S; Mol wt: 503.2422

ACTION – Cannabinoid CB₂ receptor antagonist reported to exhibit > 400-fold selectivity for CB₂ over CB₁ receptors and oral activity *in vivo* (ED₅₀ < 20 mg/kg). Potentially useful for the treatment of a broad range of CB₂-mediated disorders including but not limited to autoimmune diseases, psoriasis, lupus erythematosus, arthritis, amyotrophic lateral sclerosis, transplant rejection, allergies, bacterial, viral and protozoal infections, inflammatory disorders, irritable bowel syndrome, osteoporosis, pain, ocular or pulmonary disorders, neurodegenerative diseases, migraine, cardiovascular diseases, cancer, gastrointestinal disorders, obesity, etc. Other exemplified 3-arylindole derivatives are:



Compound	R1	R2	R3	R4	Formula
322197	H	Br	2,3-(Cl)2-Ph	SEt	C ₂₀ H ₁₈ BrCl ₂ NOS
322199	H	Br	2,3-(Cl)2-Ph	CH ₂ NHSO ₂ Me	C ₂₀ H ₁₉ BrCl ₂ N ₂ O ₃ S
322200	Cl	Cl	2-F-3-CF ₃ -Ph	CH ₂ NHSO ₂ Me	C ₂₁ H ₁₈ Cl ₂ F ₄ N ₂ O ₃ S
322201	H	Cl	4-Br-1-Naph	CH ₂ NHSO ₂ Me	C ₂₄ H ₂₂ BrClN ₂ O ₃ S
322202	Cl	Cl	4-Br-1-Naph	CH ₂ NHSO ₂ Me	C ₂₄ H ₂₁ BrCl ₂ N ₂ O ₃ S
322203	H	Cl	2-F-3-CF ₃ -Ph	CH ₂ NHSO ₂ Et	C ₂₂ H ₂₁ ClF ₄ N ₂ O ₃ S
322204	Me	Cl	2-F-3-CF ₃ -Ph	CH ₂ NHSO ₂ Me	C ₂₂ H ₂₁ ClF ₄ N ₂ O ₃ S
322205	Cl	Me	2-F-3-CF ₃ -Ph	CH ₂ NHSO ₂ Me	C ₂₂ H ₂₁ ClF ₄ N ₂ O ₃ S

SOURCE – Sanofi-Synthelabo.

REFERENCES

1. Barth, F. et al. (Sanofi-Synthelabo) 3-Arylindole derivs. and their use as CB2 receptor agonists. WO 0242269.

HUIGMB17

321682

Humanized monoclonal antibody against interferon gamma

ACTION – Partially humanized monoclonal antibody to human interferon gamma able to block interferon gamma binding to its receptor and to suppress the antiproliferative effect of interferon gamma in sensitive cell lines. *In vivo*, the antibody given intradermally together with tuberculin in tuberculin-positive subjects was able to completely block delayed hypersensitivity reaction in the absence of adverse reactions. Potentially useful for the treatment of autoimmune disorders, myasthenia gravis, systemic lupus erythematosus, rheumatoid arthritis, diabetes and Crohn's disease.

SOURCE – Università degli Studi di Brescia, Brescia (IT).

REFERENCES

1. Fiorentini, S. et al. A partially humanized monoclonal antibody to human IFN-γ inhibits cytokine effects both in vitro and in vivo. Scand J Immunol 2002, 55(3): 284.

PERU-15

285085

Live, oral vaccine for cholera based on an attenuated motility-defective form of *Vibrio cholerae* O1 E1 Tor strain which has the entire cholera toxin (CT) genetic element and the attRS1 insertion-like sequences deleted and the gene encoding the nontoxic B subunit of CT inserted into the recA gene

CholeraGarde™

ACTION – Live attenuated oral cholera vaccine derived from a *Vibrio cholerae* O1 EI Tor Inaba strain, proven to be safe and immunogenic and to provide significant protection against moderate and severe diarrhea, as demonstrated in a randomized, placebo-controlled study

in a human volunteer cholera challenge model. Potentially useful for preventing cholera in travelers, as well as in areas where cholera is endemic.

SOURCES – Avant Immunotherapeutics; International Vaccine Institute, Seoul (KR); National Institutes of Health, Bethesda, MD (US).

REFERENCES

1. Cohen, M.B. et al. Randomized, controlled human challenge study of the safety, immunogenicity, and protective efficacy of a single dose of Peru-15, a live attenuated oral cholera vaccine. Infect Immun 2002, 70(4): 1965.

2. Kenner, J.R. et al. Peru-15, an improved live attenuated oral vaccine candidate for *Vibrio cholerae* O1. J Infect Dis 1995, 172(4): 1126.

3. Sack, D.A. et al. Alternative buffers with Peru-15, a new live oral cholera vaccine. 97th Gen Meet Am Soc Microbiol (May 4-8, Miami Beach) 1997, Abst E-101.

4. Sack, D.A. et al. Comparison of alternative buffers for use with a new live oral cholera vaccine, Peru-15, in outpatient volunteers. Infect Immun 1997, 65(6): 2107.

5. Sack, D.A. et al. Evaluation of Peru-15, a new live oral vaccine for cholera, in volunteers. J Infect Dis 1997, 176(1): 201.

6. Avant continues to advance products into later stages of clinical development. DailyDrugNews.com (Daily Essentials) 2001, Oct 30.

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8. Avant signs research agreement with International Vaccine Institute for cholera vaccine. DailyDrugNews.com (Daily Essentials) 2002, Feb 25.

9. Avant's cholera vaccine enters phase II study. DailyDrugNews.com (Daily Essentials) 2002, May 22.

10. Avant's cholera vaccine to enter phase IIB trial. DailyDrugNews.com (Daily Essentials) 2000, Jan 19.

11. Avant's oral cholera vaccine shows safety and efficacy in phase IIb trial. DailyDrugNews.com (Daily Essentials) 2001, May 9.

12. Cholera vaccine moves into phase IIb trials. DailyDrugNews.com (Daily Essentials) 2000, Oct 17.

ONCOLYTIC DRUGS

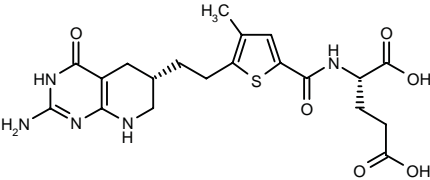
ANTIMETABOLITES

AG-2037

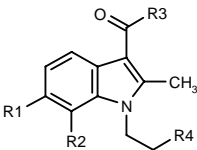
213634

N-[5-[2-[2-Amino-4-oxo-3,4,5,6,7,8-hexahydropyrido-[2,3-d]pyrimidin-6(S)-yl]ethyl]-4-methylthien-2-ylcarbonyl]-L-glutamic acid

AG-2032 (as racemate)



C20 H25 N5 O6 S; Mol wt: 463.5125



Compound	R1	R2	R3	R4	Formula
322197	H	Br	2,3-(Cl)2-Ph	SEt	C ₂₀ H ₁₈ BrCl ₂ NOS
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322200	Cl	Cl	2-F-3-CF ₃ -Ph	CH ₂ NHSO ₂ Me	C ₂₁ H ₁₈ Cl ₂ F ₄ N ₂ O ₃ S
322201	H	Cl	4-Br-1-Naph	CH ₂ NHSO ₂ Me	C ₂₄ H ₂₂ BrClN ₂ O ₃ S
322202	Cl	Cl	4-Br-1-Naph	CH ₂ NHSO ₂ Me	C ₂₄ H ₂₁ BrCl ₂ N ₂ O ₃ S
322203	H	Cl	2-F-3-CF ₃ -Ph	CH ₂ NHSO ₂ Et	C ₂₂ H ₂₁ ClF ₄ N ₂ O ₃ S
322204	Me	Cl	2-F-3-CF ₃ -Ph	CH ₂ NHSO ₂ Me	C ₂₂ H ₂₁ ClF ₄ N ₂ O ₃ S
322205	Cl	Me	2-F-3-CF ₃ -Ph	CH ₂ NHSO ₂ Me	C ₂₂ H ₂₁ ClF ₄ N ₂ O ₃ S

SOURCE – Sanofi-Synthélabo.

REFERENCES

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ONCOLYTIC DRUGS

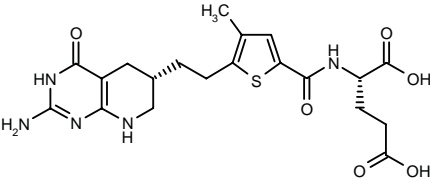
ANTIMETABOLITES

AG-2037

213634

N-[5-[2-[2-Amino-4-oxo-3,4,5,6,7,8-hexahydropyrido-[2,3-d]pyrimidin-6(S)-yl]ethyl]-4-methylthien-2-ylcarbonyl]-L-glutamic acid

AG-2032 (as racemate)



C20 H25 N5 O6 S; Mol wt: 463.5125

ACTION – Potent and selective antifolate inhibitor of glycinamide ribonucleotide formyltransferase (GARFT, phosphoribosylglycinamide formyltransferase; $K_i = 0.4\text{--}0.5$ nM) with high selectivity over the membrane folate-binding protein. Compound is able to enter cells by the reduced folate carrier and is a substrate for folypolyglutamate synthetase (FPGS). Compound exhibited significant cytotoxic effects against tumor cells *in vitro* and against murine tumor systems and human xenografts *in vivo*; it retained excellent antitumor activity in the low folate mouse model over a wide range of concentrations. Results of phase I clinical trials in patients with advanced cancers showed linear pharmacokinetics and a correlation between total plasma clearance and creatinine clearance. Dose-limiting toxicity included grade 3 hyperbilirubinemia, anemia, thrombocytopenia, grade 3 fatigue, mucositis and thrombocytopenia.

SOURCE – Agouron (Pfizer).

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8. Faessel, H. et al. *Super in vitro synergy between trimetrexate and the polyglutamylatable antifolates AG2034, AG2032, AG2009 and Tomudex against human HCT-8 colon cells.* Proc Am Assoc Cancer Res 1996, 37: Abst 2629.

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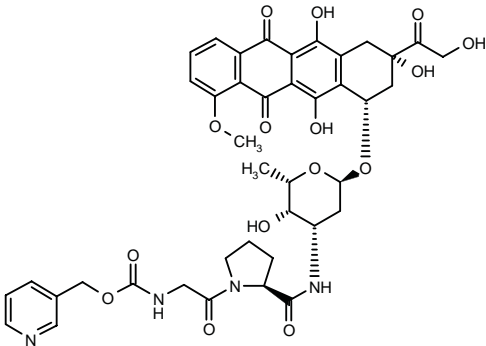
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ANTIBIOTICS AND ALKALOIDS

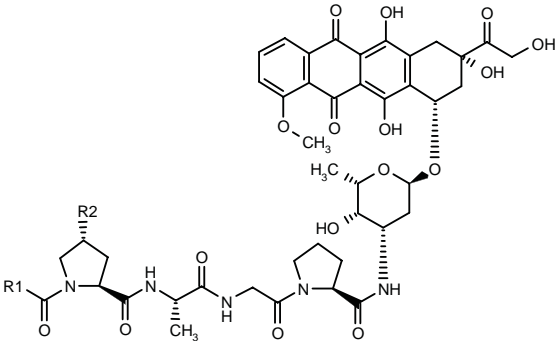
321115

N-[N-(Pyridin-3-ylmethoxycarbonyl)glycyl-L-prolyl]-doxorubicin

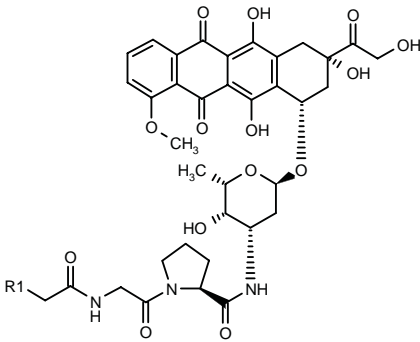


C41 H44 N4 O15; Mol wt: 832.8116

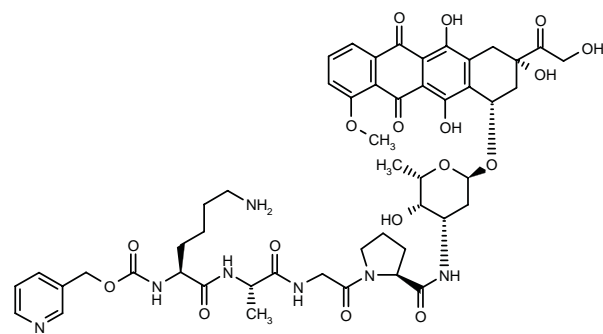
ACTION – A prodrug of doxorubicin that is converted to the active compound at the site of the tumor by the catalytic action of fibroblast activation protein $FAP\alpha$, which is expressed in cancer tissues. Other exemplified compounds are:



Compound	R1	R2	Formula
321116	3-Pyr-CH2	H	C ₄₉ H ₅₆ N ₆ O ₁₆
321119	3-Pyr-CH2O	OH	C ₄₉ H ₅₆ N ₆ O ₁₈
321121	4-morpholinyl-CH2CH2O	H	C ₄₉ H ₆₂ N ₆ O ₁₈



Compound	R1	Formula
321117	2-Pyr	C ₄₁ H ₄₄ N ₄ O ₁₄
321120	3-Pyr	C ₄₁ H ₄₄ N ₄ O ₁₄



321118: C50 H61 N7 O17

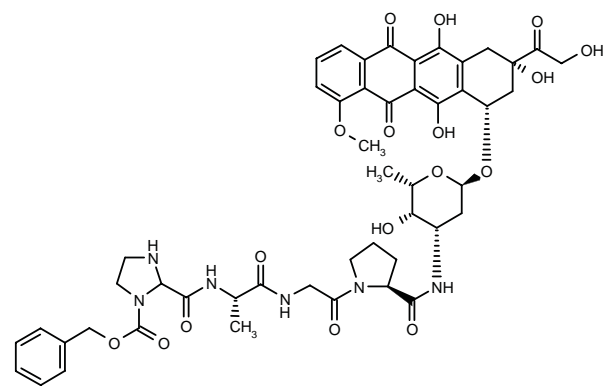
SOURCE – Boehringer Ingelheim.

REFERENCES

1. Peters, S. et al. (Boehringer Ingelheim Pharma KG) *FAP-α-activated anti-tumor cpds.* WO 0238590.

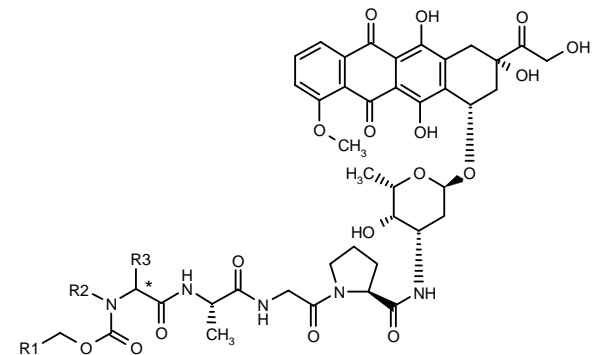
321213

N-[*N*-[1-(Benzyloxycarbonyl)imidazolidin-2-ylcarbonyl]-L-alanyl-glycyl-L-prolyl]doxorubicin



C49 H56 N6 O17; Mol wt: 1001.0060

ACTION – A prodrug of doxorubicin that is converted to the active compound at the site of the tumor by the catalytic action of fibroblast activation protein FAPα, which is expressed in cancer tissues. Other exemplified compounds are:



Compound	R1	R2,R3	*Isomer	Formula
321214	3-Pyr	-CH2CH2NH-		C ₄₈ H ₅₅ N ₇ O ₁₇
321215	Ph	-CH2CH2NHCH2-		C ₅₀ H ₅₈ N ₆ O ₁₇
321216	3-Pyr	-CH2CH2NHCH2-		C ₄₉ H ₅₇ N ₇ O ₁₇
321217	Ph	-CH2CH2OCH2-		C ₅₀ H ₅₇ N ₅ O ₁₈
321218	Ph	-CH2SCH2-	R	C ₄₉ H ₅₅ N ₅ O ₁₇ S

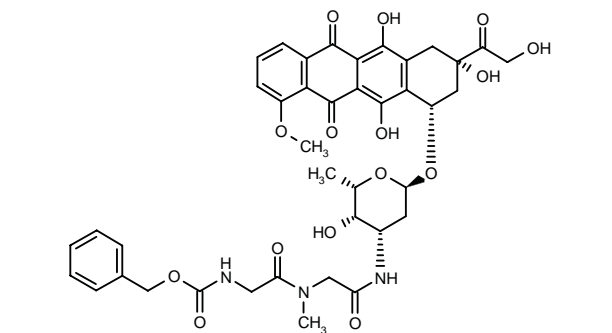
SOURCE – Boehringer Ingelheim.

REFERENCES

1. Peters, S. et al. (Boehringer Ingelheim Pharma KG) *FAP-activated anti-tumor cpds.* WO 0238591.

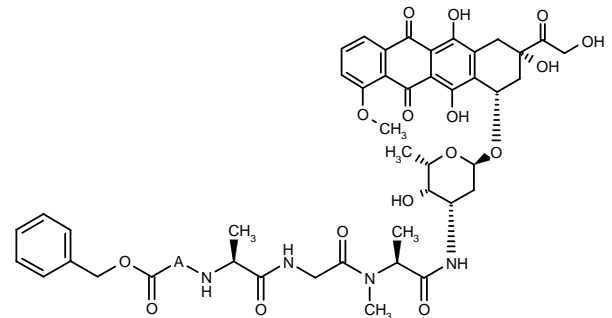
321221

N-[*N*-(Benzyloxycarbonyl)glycyl-*N*-methylglycyl]-doxorubicin

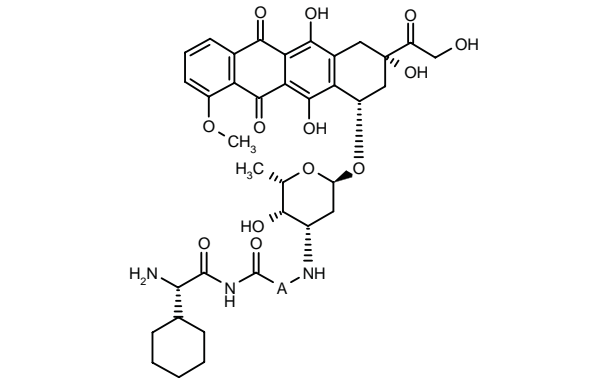


C40 H43 N3 O15; Mol wt: 805.7857

ACTION – A prodrug of doxorubicin that is converted to the active compound at the site of the tumor by the catalytic action of fibroblast activation protein FAPα, which is expressed in cancer tissues. Other exemplified compounds are:



Compound	A	Formula
321222	-L-Pro-	C ₄₉ H ₅₇ N ₅ O ₁₇
321225	-L-Lys-	C ₅₀ H ₆₂ N ₆ O ₁₇
321227	4(R)-OH-L-Pro-	C ₄₉ H ₅₇ N ₅ O ₁₈



Compound	A	Formula
321223	-D-N-Me-Ala-	C ₄₀ H ₅₀ N ₄ O ₁₄
321224	-L-N-Me-Val-	C ₄₂ H ₅₄ N ₄ O ₁₄

SOURCE – Boehringer Ingelheim.

REFERENCES

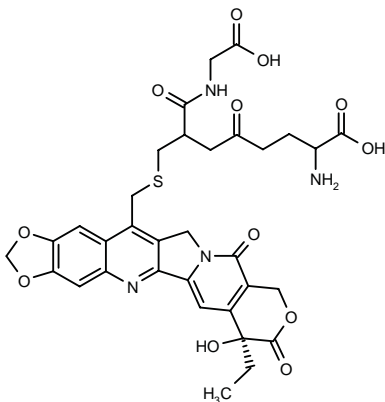
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DNA-INTERCALATING DRUGS

321877

2-Amino-7-[*N*-(carboxymethyl)carbamoyl]-8-[7(*S*)-ethyl-7-hydroxy-8,11-dioxo-8,10,11,13-tetrahydro-7*H*-[1,3]-dioxolo[4,5-*g*]pyrano[3',4':6,7]indolizino[1,2-*b*]quinolin-14-ylmethylsulfanyl]-5-oxooctanoic acid

7-[7-Amino-7-carboxy-2-[*N*-(carboxymethyl)carbamoyl]-4-oxoheptylsulfanylmethyl]-10,11-(methylenedioxy)camptothecin



C33 H34 N4 O12 S; Mol wt: 710.7136

ACTION – Camptothecin derivative that inhibits DNA topoisomerase I and is thus potentially useful for the treatment of solid tumors and leukemia. It was cytotoxic to P388 leukemia cells at 0.1 μM and showed an IC₅₀ of 20 nM against U-937 leukemia cells.

SOURCES – Duke University, Durham, NC (US); National Institutes of Health, Bethesda, MD (US); Research Triangle Institute, Research Triangle Park, NC (US).

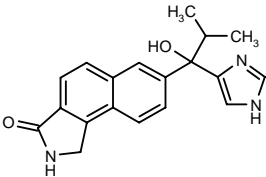
REFERENCES

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HORMONAL AGENTS

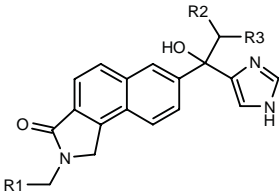
321739

7-[1-Hydroxy-1-(1*H*-imidazol-4-yl)-2-methylpropyl]-2,3-dihydro-1*H*-benzo[*e*]isoindol-3-one

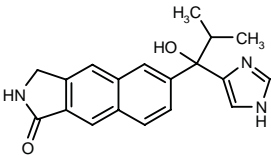


C19 H19 N3 O2; Mol wt: 321.3781

ACTION – Steroid 17-α-monooxygenase (steroid 17-α-hydroxylase/17,20 lyase) inhibitor (IC₅₀ < 10 nM) with > 1,000-fold selectivity over CYP3A4. *In vivo*, it was able to inhibit the biosynthesis of testosterone in rats (T/C = 6.0% at 25 mg/kg p.o.). Potentially useful for the treatment of cancer, as well as prostatic hypertrophy, virilism, hypertrichosis, male pattern baldness, male precocity, endometriosis, uterine leiomyoma, mastopathy and polycystic ovary syndrome. Other exemplified imidazole derivatives are:



Compound	R1	R2	R3	Isomer	Formula
321740	H	Me	Me		C ₂₀ H ₂₁ N ₃ O ₂
321741	Me	Me	Me		C ₂₁ H ₂₃ N ₃ O ₂
321743	H	H	i-Pr		C ₂₁ H ₂₃ N ₃ O ₂
321744	H	Me	Me	(-)	C ₂₀ H ₂₁ N ₃ O ₂



321742: C19 H19 N3 O2

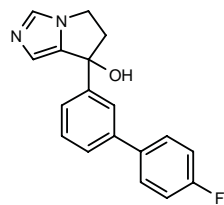
SOURCE – Takeda.

REFERENCES

1. Tasaka, A. et al. (Takeda Chemical Industries, Ltd.) *Imidazole derivs., process for their preparation and their use*. WO 0240470.

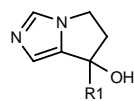
321878

7-(4'-Fluorobiphenyl-3-yl)-6,7-dihydro-5H-pyrrolo[1,2-c]-imidazol-7-ol



C18 H15 F N2 O; Mol wt: 294.3275

ACTION – Steroid 17- α -monooxygenase (steroid 17- α -hydroxylase/17-20 lyase) inhibitor (IC_{50} = 10 nM) with 960-fold selectivity over cytochrome P-450 CYP3A4. *In vivo*, compound was shown to inhibit the biosynthesis of testosterone following oral administration to rats at a dose of 25 mg/kg (T/C = 4.4%). Potentially useful for the treatment of tumors, particularly prostate and breast cancer. Other imidazole derivatives are:



Compound	R1	Isomer	Formula
321879	4-(4-F-Ph)-Ph		C ₁₈ H ₁₅ FN ₂ O
321880	6-(MeNHCO)-2-Naph		C ₁₈ H ₁₇ N ₃ O ₂
321881	6-(MeNHCO)-2-Naph	(+)	C ₁₈ H ₁₇ N ₃ O ₂

SOURCE – Takeda.

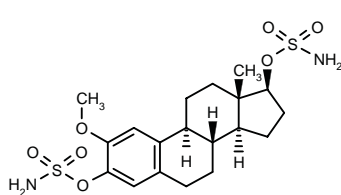
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1. Tasaka, A. et al. (Takeda Chemical Industries, Ltd.) *Novel imidazole derivs., production method thereof and use thereof.* WO 0240484.

2-MeOE2BISMATE¹⁻³

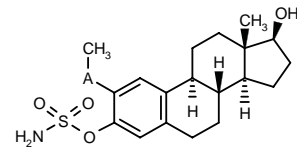
321855

Bis(sulfamic acid) 17(β)-hydroxy-2-methoxyestra-1,3,5(10)-triene-3,17-diyl diester



C19 H28 N2 O7 S2; Mol wt: 460.5692

ACTION – Site-directed inhibitor of steroid sulfatase (IC_{50} = 32 nM in placental microsomes), able to inhibit the growth of MDA-MB-231 cells and to induce an irreversible arrest in the G₂M phase of the cell cycle and apoptosis within 24 h. In addition, compound, was equipotent to colchicine in inhibiting paclitaxel-induced microtubule polymerization in bovine brains. Potentially useful for the treatment of breast cancer. Other related compounds are:



Compound	A	Formula
2-MeOE2MATE [321854] ^{2,3}	O	C ₁₉ H ₂₇ NO ₅ S
2-EtE2MATE [321857] ^{2,3}	CH2	C ₂₀ H ₂₉ NO ₄ S

SOURCE – Sterix.

REFERENCES

1. Potter, B.V.L. and Reed, M.J. (Sterix Ltd.) *17-Aryl-linker derivatised estrogen 3-sulphamates as inhibitors of steroid sulphatase.* WO 0216393.

2. Potter, B.V.L. and Reed, M.J. (Sterix Ltd.) *Oestrogen-17-sulphamates as inhibitors of steroid sulphatase.* WO 0216392.

3. Reed, M.J. et al. *2-Methoxyestrogen sulfamates are potent inhibitors of steroid sulfatase activity and estrogen receptor negative breast cancer growth.* 84th Annu Meet Endocr Soc (June 19-22, San Francisco) 2002, Abst P1-647.

CANCER IMMUNOTHERAPY

322309

Doxorubicin conjugated to NL-1 MAb targeted to common acute lymphoblastic leukemia antigen (CALLA, CD10) via the polyethylene glycol (PEG) dipeptidyl linker L-Pro-Gly-PEG

ACTION – Antineoplastic immunoconjugate consisting of doxorubicin linked to a monoclonal antibody against the Daudi cell tumor-specific antigen CALLA (CD10) via a polyethylene glycol (PEG)-based cleavable dipeptide linker. In Daudi cells, the immunoconjugate was cleaved selectively by tumor-specific enzyme to express the cytotoxic activity of doxorubicin. The conjugate retained a significant and concentration-dependent effect only for target cells: its cytotoxicity was approximately 3-fold lower than that of doxorubicin alone in Daudi cells (IC_{50} = 4.5 μ g/ml and 17 nM, respectively) and it was inactive in HeLa cells. *In vivo*, in mice bearing CD10⁺ myeloma SK-LY-18 cells, the immunoconjugate reduced tumor growth by 50% after 25 days of treatment. Another related immunoconjugate is:

Doxorubicin conjugated to NL-1 MAb targeted to common acute lymphoblastic leukemia antigen (CALLA, CD10) via the polyethylene glycol (PEG)-dipeptide linker L-Val-L-Ala-PEG

322310

SOURCE – Kyowa Hakko.

REFERENCES

1. Suzawa, T. et al. (Kyowa Hakko Kogyo Co., Ltd.) *Toxin conjugates.* EP 0867190, US 6103236, WO 9635451.

2. Suzawa, T. et al. *Enhanced tumor cell selectivity of adriamycin-monoconal antibody conjugate via a poly(ethylene glycol)-based cleavable linker.* J Control Release 2002, 79(1-3): 229.

3. Suzawa, T. et al. *Tumor-specific activation of a novel immunoconjugate using polyethylene glycol-dipeptidyl linker.* Jpn J Cancer Res 2000, 91(Suppl.): Abst 2170.

322320

Star conjugate of doxorubicin bound to N-(2-hydroxypropyl)methacrylamide (HPMA) copolymer via a Gly-Phe-(D,L)-Leu-Gly spacer and using as a targeting moiety the B1 MAb directed against the idiotype of surface IgM of BCL₁ cells

ACTION – Antibody-targeted doxorubicin conjugate consisting of an HPMA copolymer bound to doxorubicin via a tetrapeptidic spacer targeted with a monoclonal antibody against the idiotype of surface IgM of BCL₁ cells. The targeted conjugate exhibited higher cytostatic activity against murine leukemia BCL₁ cells than nontargeted HPMA copolymer-bound doxorubicin (CC₅₀ = 10.5 and 1450 nM, respectively). In mice bearing BCL₁ cells, the antibody-targeted conjugate (100 µg) strongly prolonged the survival of mice compared to doxorubicin alone.

SOURCE – Academy of Sciences of the Czech Republic, Prague (CZ).

REFERENCES

1. Kovar, M. et al. *Star structure of antibody-targeted HPMA copolymer-bound doxorubicin: A novel type of polymeric conjugate for targeted drug delivery with potent antitumor effect.* Bioconjugate Chem 2002, 13(2): 206.

ANTI-CD20 X ANTI-CD3 DIABODY

322322

Bispecific anti-CD20 and anti-CD3 diabody constructed from the monoclonal antibodies HI47 (against CD20) and HIT3a (against CD3)

ACTION – Anti-CD20 x anti-CD3 bispecific diabody able to crosslink CD20-positive tumor cells and CD3-positive human T-cells and to mediate lysis of human B-lymphoma cells in the presence of T-cell-enriched human peripheral blood lymphocytes. In mice bearing B-cell lymphoma Raji cells, the diabody given in combination with IL-2-pre-activated human peripheral blood lymphocytes plus IL-2 significantly prolonged survival of the mice (100 days in 3/5 mice). Potentially useful for the treatment of CD20-positive B-cell tumors.

SOURCES – Chinese Academy of Medical Sciences, Beijing (CN); Hong Kong University of Science and Technology, Kowloon (HK).

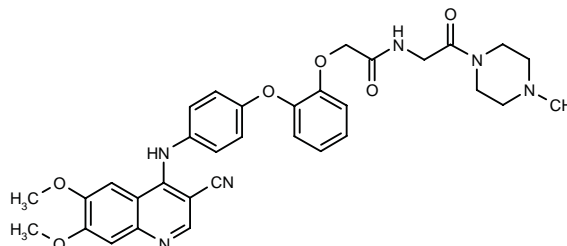
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1. Xiong, D.S. et al. *Efficient inhibition of human B-cell lymphoma xenografts with an anti-CD20 x anti-CD3 bispecific diabody.* Cancer Lett 2002, 177(1): 29.

INHIBITORS OF SIGNAL TRANSDUCTION PATHWAYS

321326

2-[2-[4-(3-Cyano-6,7-dimethoxyquinolin-4-ylamino)-phenoxy]phenoxy]-N-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]acetamide



C33 H34 N6 O6; Mol wt: 610.6676

ACTION – Mitogen ERK kinase (MEK) inhibitor with antitumor activity, shown to inhibit MEK-induced MAP kinase activation *in vitro* with an IC₅₀ of 0.0038 µM. In addition, compound inhibited the proliferation of human colon adenocarcinoma HT-29 cells with an IC₅₀ of 1.0 µM.

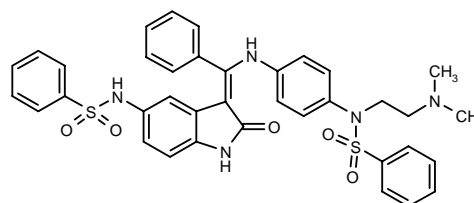
SOURCE – AstraZeneca.

REFERENCES

1. Boyle, F.T. and Gibson, K.H. (AstraZeneca AB;AstraZeneca plc) *4-Substd. quinolines as antitumor agents.* WO 0236570.

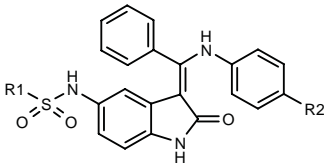
321360

(Z)-N-[2-(Dimethylamino)ethyl]-N-[4-[1-[2-oxo-5-(phenylsulfonamido)-2,3-dihydro-1H-indol-3-ylidene]-1-phenylmethylamino]phenyl]benzenesulfonamide



C37 H35 N5 O5 S2; Mol wt: 693.8455

ACTION – A representative compound from a series of inhibitors of receptor and nonreceptor tyrosine kinases and serine/threonine kinases with potential as an antitumor agent. It demonstrated *in vitro* antiproliferative activity against leiomyosarcoma SK-UT-1B cells, with an IC₅₀ < 0.01 µM. Other exemplified indolinone derivatives are:



Compound	R1	R2	Formula
321361	Ph	N(COEt)CH2CH2NHCOEt	C ₃₅ H ₃₅ N ₅ O ₅ S
321362	Ph	CH2N(Me)2	C ₃₀ H ₂₈ N ₄ O ₃ S
321363	Ph	1-Pip-CH2CON(Me)	C ₃₅ H ₃₅ N ₅ O ₄ S
321364	3-NO2-Ph	2,6-(Me)2-1-Pip-CH2	C ₃₅ H ₃₅ N ₅ O ₅ S
321365	3-Pyr	1-pyrrolidinyl-CH2	C ₃₁ H ₂₉ N ₅ O ₃ S
321366	Et	1-Pip-CH2	C ₂₉ H ₃₂ N ₄ O ₃ S
321367	i-Pr	1-Pip-CH2	C ₃₀ H ₃₄ N ₄ O ₃ S
321368	1-Naph	1-Pip-CH2	C ₃₇ H ₃₄ N ₄ O ₃ S
321369	3-NO2-Ph	1-Pip-CH2	C ₃₃ H ₃₁ N ₅ O ₅ S
321370	cyclopropyl	1-Pip-CH2	C ₃₀ H ₃₂ N ₄ O ₃ S
321371	3-Pyr	1-Pip-CH2	C ₃₂ H ₃₁ N ₅ O ₃ S
321372	4-NH2-Ph	1-Pip-CH2	C ₃₃ H ₃₃ N ₅ O ₃ S

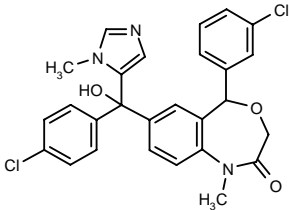
SOURCE – Boehringer Ingelheim.

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1. Walter, R. et al. (Boehringer Ingelheim Pharma KG) *Sulfonamino subst. 3-(aminomethylide)-2-indolinones as cell proliferation inhibitors*. DE 10054019, WO 0236564.

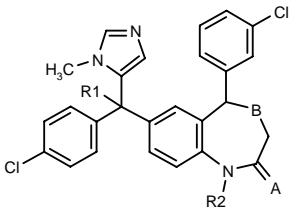
322115

5-(3-Chlorophenyl)-7-[1-(4-chlorophenyl)-1-hydroxy-1-(1-methyl-1*H*-imidazol-5-yl)methyl]-1-methyl-1,2,3,5-tetrahydro-4,1-benzoxazepin-2-one

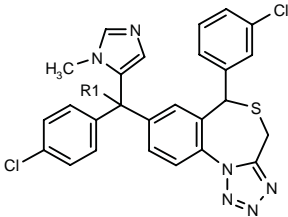


C27 H23 Cl2 N3 O3; Mol wt: 508.4027

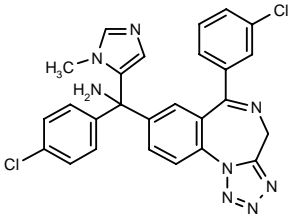
ACTION – Protein farnesyltransferase inhibitor with anti-tumor activity. Other specifically claimed benzoheterocyclic derivatives are:



Compound	R1	R2	A	B	Formula
322116	OH	Me	O	-S-	C ₂₇ H ₂₃ Cl ₂ N ₃ O ₂ S
322117	OH	H	S	-O-	C ₂₆ H ₂₁ Cl ₂ N ₃ O ₂ S
322118	NH2	Me	O	-S-	C ₂₇ H ₂₄ Cl ₂ N ₄ OS
322120	H	H	O	-S-	C ₂₆ H ₂₁ Cl ₂ N ₃ OS
322123	H	H	O	-SCH2-	C ₂₇ H ₂₃ Cl ₂ N ₃ OS



Compound	R1	Formula
322121	NH2	C ₂₆ H ₂₁ Cl ₂ N ₇ S
322122	H	C ₂₆ H ₂₀ Cl ₂ N ₆ S



322119: C26 H20 Cl2 N8

SOURCE – Janssen.

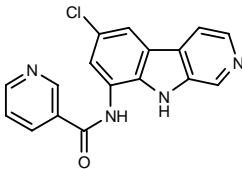
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1. Angibaud, P.R. et al. (Janssen Pharmaceutica NV) *Farnesyl transferase inhibiting benzoheterocyclic derivs*. WO 0242296.

PS-1145*

310461

N-(6-Chloro-9*H*-pyrido[3,4-*b*]indol-8-yl)pyridine-3-carboxamide



C17 H11 Cl N4 O; Mol wt: 322.7539

ACTION – Potent and selective IκB kinase (IKK) inhibitor (K_i = 88 nM) able to concentration- and time-dependently inhibit TNF-α-induced nuclear factor NF-κB activation in multiple myeloma cells via inhibition of IκBα phosphorylation and degradation; this effect was blocked by dexamethasone which upregulated IκBα expression. Moreover, compound inhibited TNF-α-induced up-regulation of ICAM-1 expression on multiple myeloma cells and suppressed the induction of IL-6 secretion from bone marrow stromal cells triggered by multiple myeloma cell adhesion, as well as the increased proliferation of adherent multiple myeloma cells. Compound showed only a partial direct antiproliferative effect against multiple myeloma cells (20-50% inhibition at > 12.5 μM), indicating that the compound was able to suppress the increased tumor cell growth and survival via inhibition of NF-κB activation.

SOURCE – Aventis Pharma.

REFERENCES

1. Ritzeler, O. et al. (Aventis Pharma Deutschland GmbH) *Substd. β-carbolines as IκB-kinase inhibiting activity*. EP 1134221, EP 1209158, WO 0168648.

2. Gao, W. et al. *Inhibition of IκB kinase (IKK) in transplantation*. Am J Transplant 2001, 1(Suppl. 1): Abst 531.

3. Hideshima, T. et al. *NF-κB as a therapeutic target in multiple myeloma (MM)*. Blood 2001, 98(11, Part 1): Abst 1581.

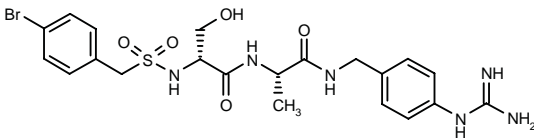
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*Identified compound **310461** Drug Data Rep 2002, 024(01): 0031.

ANGIOGENESIS INHIBITORS

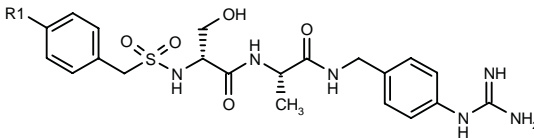
321240

N-(4-Bromobenzylsulfonyl)-D-seryl-N¹-(4-guanidino-benzyl)-L-alaninamide



C21 H27 Br N6 O5 S; Mol wt: 555.4513

ACTION – Urokinase-type plasminogen activator (uPA) inhibitor (IC₅₀ = 1.6 nM) with high selectivity over human trypsin (IC₅₀ = 42.8 nM). Potentially useful for the treatment of cancer. Other related compounds are:



Compound	R1	Formula
321239	Cl	C ₂₁ H ₂₇ ClN ₆ O ₅ S
321242	I	C ₂₁ H ₂₇ I N ₆ O ₅ S

SOURCE – Corvas.

REFERENCES

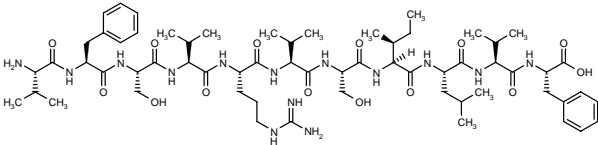
1. Levy, O.E. et al. (Corvas International, Inc.) *Non-covalent inhibitors of urokinase and blood vessel formation*. EP 1182207, WO 0214349.

2. Tamiz, A.P. et al. *Synthesis and biological activity of non-transition state urokinase inhibitors*. 28th Natl Med Chem Symp (June 8-12, San Diego) 2002, Abst 59.

chANG

321050

L-Valyl-L-phenylalanyl-L-seryl-L-valyl-L-arginyl-L-valyl-L-seryl-L-isoleucyl-L-leucyl-L-valyl-L-phenylalanine



C62 H100 N14 O14; Mol wt: 1265.5560

ACTION – Angiogenesis inhibitor, an antiangiogenin peptide that binds to the actin binding site of angiogenin and inhibits the proteolytic activity of plasmin without any apparent effect on the activities of plasminogen activators and matrix metalloproteinases. *In vitro*, compound inhibited the invasion of angiogenin-secreting human fibrosarcoma cells and blocked the angiogenesis induced by fibrosarcoma cells. *In vivo* in a mouse model of liver metastasis compound (2.5 μg/day s.c. for 21 days) potently reduced the number of liver metastases and the weight of the liver.

SOURCES – Chungnam National University, Taejon (KR); Kyung Hee University, Seoul (KR); Pohang University of Science and Technology, Pohang (KR).

REFERENCES

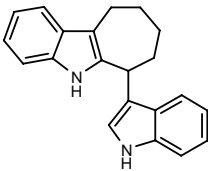
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2. Gho, Y.S. et al. *Antiplasmin activity of a peptide that binds to the receptor-binding site of angiogenin*. J Biol Chem 2002, 277(12): 9690.

ST-1381

321189

6-(1*H*-Indol-3-yl)-5,6,7,8,9,10-hexahydrocyclohepta[*b*]-indole



C21 H20 N2; Mol wt: 300.4030

ACTION – A representative compound from a group of tricyclic indole derivatives for use in the treatment of disorders associated with abnormal angiogenesis such as cancer, arthritis, diabetic retinopathy, psoriasis, chronic inflammatory diseases and arteriosclerosis. ST-1381 was able to inhibit the proliferation of MCF7 (human mammary carcinoma) and LoVo cells (human colon carcinoma) with respective IC₅₀ values of 28.5 and 22.5 μM. It arrested cells in the G₀/G₁ phase and was not cytotoxic to endothelial cells (IC₅₀ > 100 μM).

SOURCE – Sigma-Tau.

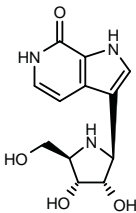
REFERENCES

1. Giannini, G. et al. (Sigma-Tau Industrie Farmaceutiche Riunite SpA) *Tricyclic derivs. of indole with antiangiogenic activity*. WO 0236597.

OTHER ONCOLYTIC DRUGS

321141

3-[3(*S*),4(*R*)-Dihydroxy-5(*R*)-(hydroxymethyl)pyrrolidin-2(*S*)-yl]-6,7-dihydro-1*H*-pyrrolo[2,3-*c*]pyridin-7-one



C12 H15 N3 O4; Mol wt: 265.2675

ACTION – A representative compound from a series of 3-hydroxypyrrolidine derivatives that act as inhibitors of purine-nucleoside phosphorylase. Compounds of the invention are therefore able to prevent T-cell proliferation and may have potential in the treatment of a number of cancers including leukemia, lymphomas, Hodgkin’s disease, multiple myeloma and solid tumors such as brain, colon, renal and mammary tumors.

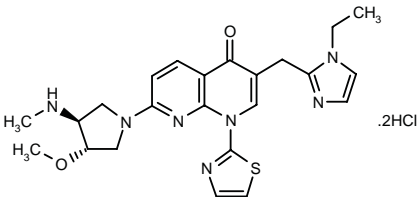
SOURCE – BioCryst.

REFERENCES

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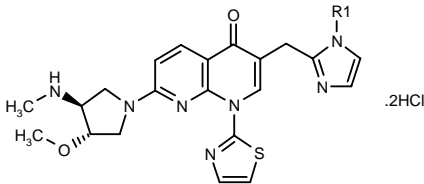
321142

3-(1-Ethyl-1*H*-imidazol-2-ylmethyl)-7-[3(*S*)-methoxy-4(*S*)-(methylamino)pyrrolidin-1-yl]-1-(2-thiazolyl)-1,8-naphthyridin-4(1*H*)-one dihydrochloride



C23 H27 N7 O2 S . 2HCl; Mol wt: 538.5011

ACTION – Antitumor agent with IC₅₀ values of 0.00174 and 0.00402 µg/ml, respectively, against P388 and KB cancer cell lines. In acute toxicity tests, no deaths were observed following administration to mice at a dose of 60 mg/kg i.v. Other exemplified 1,8-naphthyridine derivatives are:



Compound	R1	Formula
321144	H	C ₂₁ H ₂₃ N ₇ O ₂ S.2HCl
321145	CH2Ph	C ₂₈ H ₃₉ N ₇ O ₂ S.2HCl

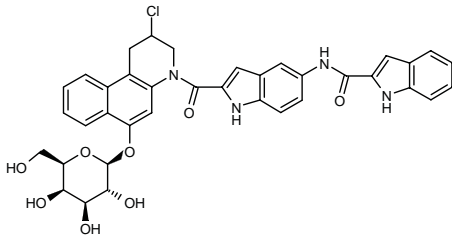
SOURCE – Dainippon Pharmaceutical.

REFERENCES

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321343

N-[2-[2-Chloro-6-(β-D-galactopyranosyloxy)-1,2,3,4-tetrahydrobenzo[*f*]quinolin-4-ylcarbonyl]-1*H*-indol-5-yl]-1*H*-indole-2-carboxamide



C37 H33 Cl N4 O8; Mol wt: 697.1407

ACTION – Nontoxic prodrug suitable for use in the antibody-directed enzyme prodrug therapy (ADEPT) of cancer; in the presence of β-D-galactosidase, the prodrug is converted to a highly cytotoxic analogue of CC-1065. *In vitro*, the prodrug in the presence of β-D-galactosidase exhibited subnanomolar cytotoxicity against human lung carcinoma A549 and human pancreatic adenocarcinoma PancTu 1 cell lines (IC₅₀ = 0.20 and 0.13 nM, respectively), whereas it was much less cytotoxic in the absence of β-D-galactosidase. No acute toxicity was observed in SCID mice at therapeutic doses, indicating that it is not converted to the active compound in normal organs. In SCID mice bearing human lung and pancreatic tumor xenografts, treatment with an immuno-conjugate of galactosidase and a human epithelial mono-clonal antibody, followed by the galactoside prodrug, resulted in a significant decrease in the volume and invasion of primary tumors.

SOURCE – Georg-August-Universität Göttingen, Göttingen (DE).

REFERENCES

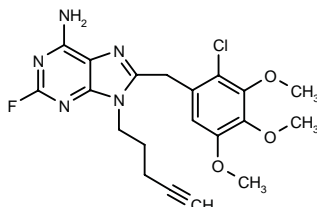
1. Tietze, L.F. et al. *Novel prodrugs of 6-hydroxy-2,3-dihydro-1H-indoles, 5-hydroxy-1,2-dihydro-3H-pyrrolo[3,2-*e*]indoles and 5-hydroxy-1,2-dihydro-3H-benzo[*e*]indoles as well as of 6-hydroxy-1,2,3,4-tetrahydro-benzo[*f*]quinoline derivs. for use in selective cancer therapy*. WO 0183448.

2. Tietze, L.F. et al. *Proof of principle in the selective treatment of cancer by antibody-directed enzyme prodrug therapy: The development of a highly potent prodrug*. Angew Chem. Int Ed 2002, 41(5): 759.

321354

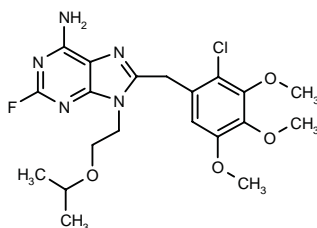
8-(2-Chloro-3,4,5-trimethoxybenzyl)-2-fluoro-9-(4-pentyn-yl)-9H-purin-6-amine

8-(2-Chloro-3,4,5-trimethoxybenzyl)-2-fluoro-9-(4-pentyn-yl)adenine



C20 H21 Cl F N5 O3; Mol wt: 433.8689

ACTION – Agent with the ability to bind to heat shock protein 90 (Hsp90) exhibiting antiproliferative activity against the human breast cancer cell lines MCF7, Her2/MCF7, BT-474 and MDA-MB-468. Another exemplified compound is:



321355: C20 H25 Cl F N5 O4

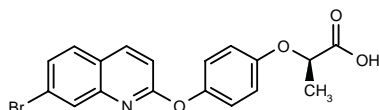
SOURCE – Sloan-Kettering Institute, New York, NY (US).

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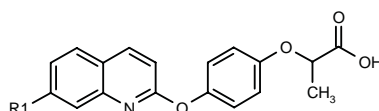
321497

2(R)-[4-(7-Bromoquinolin-2-yloxy)phenoxy]propionic acid



C18 H14 Br N O4; Mol wt: 388.2156

ACTION – Antineoplastic agent with *in vivo* antitumor activity in mice bearing pancreatic ductal adenocarcinoma Panc 03 tumors and multidrug-resistant mammary adenocarcinoma Mam17/adr. Selected as a candidate for phase I clinical trials. Other related compounds are:



Compound	R1	Isomer	Formula
321496	Cl	R	C ₁₈ H ₁₄ ClNO ₄
321498	OMe	racemic	C ₁₉ H ₁₇ NO ₅

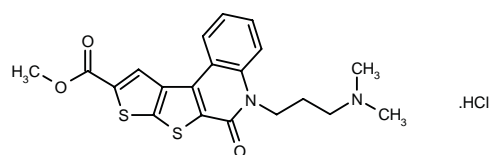
SOURCES – Karmanos Cancer Institute, Detroit, MI (US); Walker Cancer Research Institute, Aberdeen, MD (US); Wayne State University, Detroit, MI (US).

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321773

5-[3-(Dimethylamino)propyl]-6-oxo-5,6-dihydrothieno-[3',2':4,5]thieno[2,3-c]quinoline-9-carboxylic acid methyl ester hydrochloride



C20 H20 N2 O3 S2 . HCl; Mol wt: 436.9819

ACTION – Quinolone antineoplastic agent with cytostatic activity against a panel of human cancer cell lines including pancreatic carcinoma MIA PaCa-2, breast carcinoma MCF7, cervical carcinoma HeLa, colon carcinoma Caco-2, laryngeal carcinoma HEP-2 and melanoma HBL cells (IC₅₀ = 1.0, 6.23, 2.2, 1.0, 2.5 and 6.17 μM, respectively).

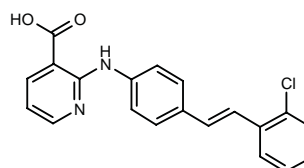
SOURCES – Rudjer Boskovic Institute, Zagreb (HR); University of Zagreb, Zagreb (HR).

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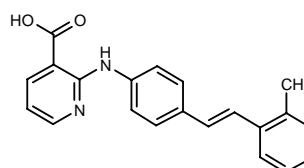
321860

2-[4-[2-(2-Chlorophenyl)vinyl]phenylamino]pyridine-3-carboxylic acid



C20 H15 Cl N2 O2; Mol wt: 350.8035

ACTION – Antitumor agent with low toxicity to normal cells, giving an IC₅₀ of 1.1 μM against human fibrosarcoma HT-1080 cells. *In vivo*, it dose-dependently inhibited the growth of B16 melanoma transplanted s.c. in mice following oral administration (86% inhibition at 60 mg/kg/day for 11 days). Another exemplified compound is:



321861: C21 H18 N2 O2

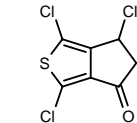
SOURCE – Chugai.

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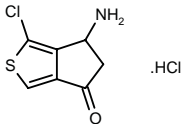
321940

1,3,6-Trichloro-5,6-dihydro-4*H*-cyclopenta[*c*]thiophen-4-one



C7 H3 Cl3 O S; Mol wt: 241.5247

ACTION – Antineoplastic agent with *in vitro* micromolar cytotoxicity against a panel of human cancer cell lines and potential *in vivo* anticancer activity as assessed in NCI's hollow fiber assay. Another related compound is:



321938: C7 H6 Cl N O S . HCl

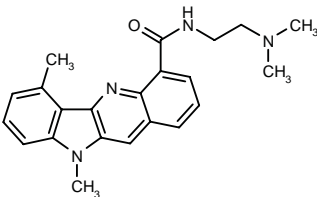
SOURCE – Université de Caen, Caen Cedex (FR).

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321966

N-[2-(Dimethylamino)ethyl]-6,10-dimethyl-10*H*-indolo-[3,2-*b*]quinoline-4-carboxamide



C22 H24 N4 O; Mol wt: 360.4586

ACTION – Antineoplastic agent, a 10*H*-quindoline derivative with *in vitro* cytotoxic activity against murine P388 leukemia cells, murine Lewis lung carcinoma and human Jurkat leukemia cells (CC₅₀= 20, 18 and 55 nM, respectively). *In vivo*, compound at the maximum tolerated dose of 65 mg/kg/day i.p. exhibited moderate growth delay of about 5 days against s.c.-implanted colon 38 tumors in mice.

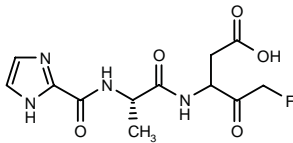
SOURCES – University of Auckland, Auckland (NZ); La Trobe University, Bundoora (AU).

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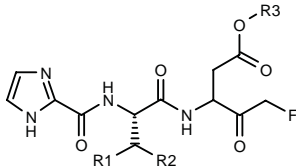
322100

5-Fluoro-3-[*N*-(1*H*-imidazol-2-ylcarbonyl)-L-alanyl-amino]-4-oxopentanoic acid

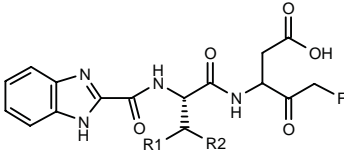


C12 H15 F N4 O5; Mol wt: 314.2715

ACTION – Caspase inhibitor, potentially useful for the treatment of a broad range of apoptosis-mediated disorders, especially cancer and complications associated with coronary artery bypass graft (CABG) surgery. Other specifically claimed compounds are:



Compound	R1	R2	R3	Formula
322101	H	H	t-Bu	C ₁₆ H ₂₃ FN ₄ O ₅
322103	H	Me	H	C ₁₃ H ₁₇ FN ₄ O ₅
322104	Me	Me	H	C ₁₄ H ₁₉ FN ₄ O ₅



Compound	R1	R2	Formula
322102	H	H	C ₁₆ H ₁₇ FN ₄ O ₅
322105	Me	Me	C ₁₈ H ₂₁ FN ₄ O ₅

SOURCE – Vertex.

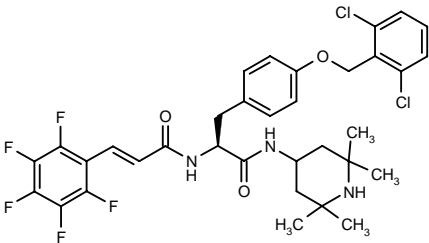
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BKM-570¹⁻³

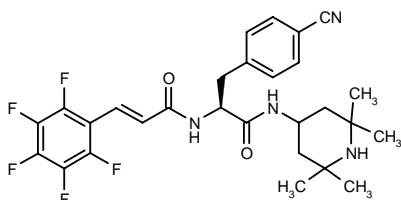
313567

O-(2,6-Dichlorobenzyl)-*N*-[3-(pentafluorophenyl)-2-propenoyl]-*N*'-(2,2,6,6-tetramethylpiperidin-4-yl)-L-tyrosinamide



C34 H34 Cl2 F5 N3 O3; Mol wt: 698.5566

ACTION – Bradykinin antagonist ($pA_2 = 5.6$ in isolated guinea pig ileum), a small peptide bradykinin mimetic with strong anticancer activity in small cell lung cancer ($IC_{50} = 0.71\text{--}1.8\text{ }\mu\text{M}$) and prostate cancer cell lines ($IC_{50} = 1.2\text{--}3.0\text{ }\mu\text{M}$). It was also active against various other human cancer cell lines *in vitro* including non-small cell lung cancer cells ($IC_{50} = 1.4\text{--}6.5\text{ }\mu\text{M}$), pancreas BxPC-3, cervix C-41, colon COLO 205 and breast ZR-75 cell lines ($IC_{50} = 0.8, 0.75, 2$ and $2.9\text{ }\mu\text{M}$, respectively). *In vivo* in mice bearing small cell lung cancer SHP-77 tumors, compound at a dose of 5 mg/kg i.p. produced 90% inhibition of tumor growth without inducing evident systemic toxicity. It was also active against prostate PC-3 cancer cells in mice. Potentially useful for the treatment of lung and prostate cancer. Another related compound is:



BKM-1110 [321967]^{1,3}: C₂₈ H₂₉ F₅ N₄ O₂

SOURCE – University of Colorado, Boulder, CO (US).

REFERENCES

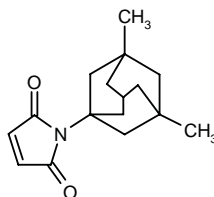
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3. Stewart, J.M. et al. *Bradykinin-related compounds as new drugs for cancer and inflammation*. Can J Physiol Pharmacol 2002, 80(4): 275.

DMAMI

261510

N-(3,5-Dimethyladamantan-1-yl)maleimide

1-(3,5-Dimethyladamantan-1-yl)-2,5-dihydro-1*H*-pyrrole-2,5-dione



C₁₆ H₂₁ N O₂; Mol wt: 259.3469

ACTION – Antineoplastic agent, an adamantylmaleimide derivative with cytotoxic activity against a panel of human cancer cells including colon carcinoma COLO 205, breast carcinoma SK-BR-3, leukemia Molt-4 and gastric carcinoma SC-M1 cells ($IC_{50} = 0.74, 0.57, 0.60$ and $0.69\text{ }\mu\text{g/ml}$, respectively). In COLO 205 cells, compound produced an arrest in the G₀/G₁ phase of the cell cycle and induced apoptosis associated with caspase 3, 8 and 9 activation. In mice bearing COLO 205 tumors, a dose of 230 mg/kg intratumorally reduced tumor incidence from 100% to 33% and tumor size from 61.2 mm^2 to 19.27 mm^2 , compared to controls.

SOURCES – National Taipei College of Nursing, Taipei (TW); National Taiwan University, Taipei (TW); National Yang-Ming University, Taipei (TW); Veterans General Hospital-Taipei, Taipei (TW).

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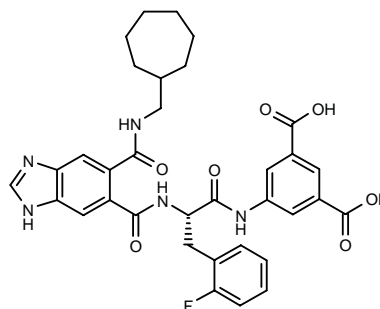
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2. Wang, J.-J. et al. *In vitro growth inhibition of human gastric cancer cells by adamantylmaleimide derivatives*. Proc Am Assoc Cancer Res 1998, 39: Abst 1547.
3. Wang, J.J. et al. *In vitro and in vivo growth inhibition of cancer cells by adamantylmaleimide derivatives*. Anti-Cancer Drug Des 1998, 13(7): 779.

GASTRAZOLE

321989

5-[*N*-[5-[*N*-(Cycloheptylmethyl)carbamoyl]-1*H*-benzimidazol-6-ylcarbonyl]-2-fluoro-L-phenylalanyl-amino]-isophthalic acid

JB-95008



C₃₄ H₃₄ F N₅ O₇; Mol wt: 643.6686

ACTION – Selective cholecystokinin CCK₂ receptor antagonist ($pK_i = 8.12$ and 5.13 for CCK₂ and CCK₁ receptor affinity, respectively), able to potently inhibit pentagastrin-stimulated gastric acid secretion in rats ($ID_{50} = 0.12\text{ }\mu\text{mol/kg/h}$), dogs ($ID_{50} = 0.03\text{ }\mu\text{mol/kg/h}$), monkeys ($ID_{50} = 0.60\text{ }\mu\text{mol/kg/h}$) and man ($ID_{50} = 0.29\text{ }\mu\text{mol/kg/h}$) following i.v. dosing. Compound exhibited poor oral availability probably due to extensive biliary elimination of unchanged drug, as seen in rats. Compound, administered i.v., is undergoing clinical trials in patients with advanced pancreatic adenocarcinoma in comparison to 5-fluorouracil. Preliminary results showed that continuous infusion of compound was well tolerated and maintained plasma levels sufficient to block CCK₂ receptors for the duration of treatment.

SOURCES – James Black Foundation;; Johnson & Johnson.J

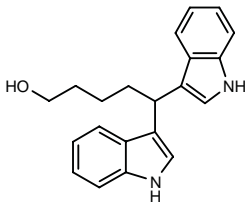
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ST-1346

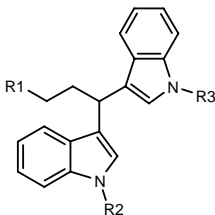
321146

5,5-Bis(1*H*-indol-3-yl)pentan-1-ol

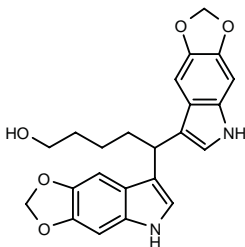


C21 H22 N2 O; Mol wt: 318.4178

ACTION – Antitumor and chemosensitizing agent shown to sensitize NB4 cells to *all-trans*-retinoic acid (ATRA)-induced differentiation. Compound was able to induce apoptosis in this cell line and in combination with ATRA resulted in a dramatic increase in cell arrest in the G₀/G₁ phase. Other exemplified bis-heterocyclic compounds are:



Compound	R1	R2	R3	Formula
ST-1707 [321147]	CH2OH	H	H	C ₂₀ H ₂₀ N ₂ O
ST-1974 [321149]	CH2CH2OH	Me	Me	C ₂₃ H ₂₆ N ₂ O
ST-1961 [321150]	CO2H	H	H	C ₂₀ H ₁₆ N ₂ O ₂



ST-1422 [321148]: C23 H22 N2 O5

SOURCE – Sigma-Tau.

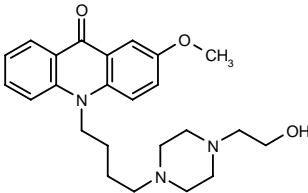
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MODULATORS OF THE THERAPEUTIC ACTIVITY OF ANTINEOPLASTIC AGENTS

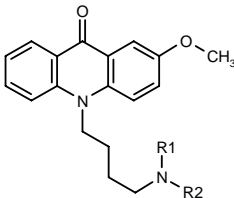
321965

10-[4-[4-(2-Hydroxyethyl)piperazin-1-yl]butyl]-2-methoxyacridin-9(10*H*)-one



C24 H31 N3 O3; Mol wt: 409.5269

ACTION – Multidrug resistance (MDR) modulator able to completely reverse the resistance of human MDR epidermoid carcinoma KBChR-8-5 cells to vinblastine. Other related compounds are:



Compound	R1	R2	Formula
321961	Et	Et	C ₂₂ H ₂₈ N ₂ O ₂
321962	-(CH2)4-		C ₂₂ H ₂₆ N ₂ O ₂
321963	-(CH2)5-		C ₂₃ H ₂₈ N ₂ O ₂
321964	-CH2CH2OCH2CH2-		C ₂₂ H ₂₆ N ₂ O ₃

SOURCES – Georgetown University, Washington, DC (US); University of Mysore, Mysore (IN); St. Jude Children’s Research Hospital, Memphis, TN (US); University of Tennessee, Memphis, TN (US).

REFERENCES

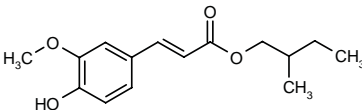
1. Krishnegowda, G. et al. *Synthesis and chemical characterization of 2-methoxy-N10-substituted acridones needed to reverse vinblastine resistance in multidrug resistant (MDR) cancer cells*. Bioorg Med Chem 2002, 10(7): 2367.

CHEMOPREVENTIVE AGENTS

FA-15

321504

3-(4-Hydroxy-3-methoxyphenyl)-2-propenoic acid 2-methylbutyl ester



C15 H20 O4; Mol wt: 264.3190

ACTION – Chemopreventive agent, a hydrophobic derivative of ferulic acid proven to suppress superoxide generation in HL-60 cells, to suppress the lipopolysaccharide- and interferon gamma-induced protein expression of inducible nitric oxide synthase (iNOS) and cyclooxygenase type 2 (COX-2) in RAW264.7 macrophages, as well as to inhibit phorbol ester-induced Epstein-Barr virus activation. *In vivo*, the topical application of compound to mouse skin significantly attenuated phorbol ester-induced hydrogen peroxide production and edema formation, as well as papilloma formation.

SOURCES – Industrial Technology Center of Wakayama Prefecture; Japan Science and Technology.

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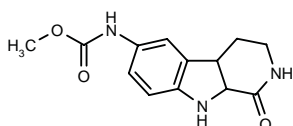
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2. Kikuzaki, H. et al. *Antioxidant properties of ferulic acid and its related compounds*. J Agric Food Chem 2002, 50(7): 2161.
3. Murakami, A. et al. *FA15, a hydrophobic derivative of ferulic acid, suppresses inflammatory responses and skin tumor promotion: Comparison with ferulic acid*. Cancer Lett 2002, 180(2): 121.
4. Murakami, A. et al. *Suppressive effects of novel ferulic acid derivatives on cellular responses induced by phorbol ester, and by combined lipopolysaccharide and interferon-gamma*. Cancer Lett 2000, 157(1): 77.

OCULAR MEDICATIONS

INS-48848

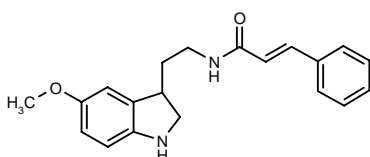
321991

N-(1-Oxo-2,3,4,4a,9,9a-hexahydro-1*H*- β -carbolin-6-yl)carbamic acid methyl ester



C13 H15 N3 O3; Mol wt: 261.2795

ACTION – Melatonin analogue able to produce a significant and long-lasting (up to 5 h) reduction in intraocular pressure in normotensive rabbits (36% reduction at 0.25 mM). The ocular tolerance test showed that compound was well tolerated in terms of ocular irritation and toxicity. Potentially useful for the treatment of glaucoma. Another related analogue is:



INS-48852 [321992]: C20 H22 N2 O2

SOURCE – Inspire Pharmaceuticals.

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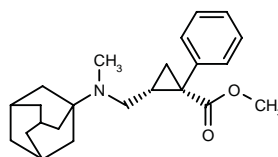
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(-)-MR-22

322056

(-)-*cis*-2-[*N*-(1-Adamantyl)-*N*-methylaminomethyl]-1-phenylcyclopropanecarboxylic acid methyl ester

(-)-*cis*-MR-22



C23 H31 N O2; Mol wt: 353.5029

ACTION – σ_1 Receptor ligand with 20-fold selectivity over σ_2 receptors ($K_i = 2.1$ and 48 nM, respectively), potentially useful for the treatment of glaucoma. In a rat model of retinal ischemia–reperfusion injury induced by elevation of intraocular pressure, compound (1 mg/kg i.p.) given before ischemia and immediately after reperfusion significantly prevented ischemia-induced retinal ganglion cell death by 80%. It also inhibited ischemia-induced biochemical changes in the retina such as the increase in lactate content and decrease in glucose. The neuro-protective effect of compound was comparable to that of flunarizine.

SOURCES – Università degli Studi di Catania, Catania (IT); Università degli Studi di Messina, Messina (IT).

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4. Ronsisvalle, G. et al. *Substituted 1-phenyl-2-cyclopropylmethylamines with high affinity and selectivity for sigma sites*. Bioorg Med Chem 2000, 8(6): 1503.

ACTION – Chemopreventive agent, a hydrophobic derivative of ferulic acid proven to suppress superoxide generation in HL-60 cells, to suppress the lipopolysaccharide- and interferon gamma-induced protein expression of inducible nitric oxide synthase (iNOS) and cyclooxygenase type 2 (COX-2) in RAW264.7 macrophages, as well as to inhibit phorbol ester-induced Epstein-Barr virus activation. *In vivo*, the topical application of compound to mouse skin significantly attenuated phorbol ester-induced hydrogen peroxide production and edema formation, as well as papilloma formation.

SOURCES – Industrial Technology Center of Wakayama Prefecture; Japan Science and Technology.

REFERENCES

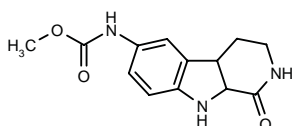
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2. Kikuzaki, H. et al. *Antioxidant properties of ferulic acid and its related compounds*. J Agric Food Chem 2002, 50(7): 2161.
3. Murakami, A. et al. *FA15, a hydrophobic derivative of ferulic acid, suppresses inflammatory responses and skin tumor promotion: Comparison with ferulic acid*. Cancer Lett 2002, 180(2): 121.
4. Murakami, A. et al. *Suppressive effects of novel ferulic acid derivatives on cellular responses induced by phorbol ester, and by combined lipopolysaccharide and interferon-gamma*. Cancer Lett 2000, 157(1): 77.

OCULAR MEDICATIONS

INS-48848

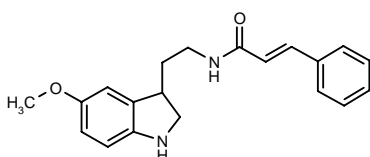
321991

N-(1-Oxo-2,3,4,4a,9,9a-hexahydro-1*H*- β -carbolin-6-yl)carbamic acid methyl ester



C13 H15 N3 O3; Mol wt: 261.2795

ACTION – Melatonin analogue able to produce a significant and long-lasting (up to 5 h) reduction in intraocular pressure in normotensive rabbits (36% reduction at 0.25 mM). The ocular tolerance test showed that compound was well tolerated in terms of ocular irritation and toxicity. Potentially useful for the treatment of glaucoma. Another related analogue is:



INS-48852 [321992]: C20 H22 N2 O2

SOURCE – Inspire Pharmaceuticals.

REFERENCES

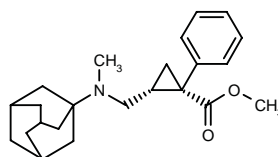
1. Plourde, R. et al. *Design of novel melatonin analogs for reduction of intraocular pressure*. Pharmacologist 2002, 44(2, Suppl. 1): Abst 32.24.

(-)-MR-22

322056

(-)-*cis*-2-[*N*-(1-Adamantyl)-*N*-methylaminomethyl]-1-phenylcyclopropanecarboxylic acid methyl ester

(-)-*cis*-MR-22



C23 H31 N O2; Mol wt: 353.5029

ACTION – σ_1 Receptor ligand with 20-fold selectivity over σ_2 receptors ($K_i = 2.1$ and 48 nM, respectively), potentially useful for the treatment of glaucoma. In a rat model of retinal ischemia–reperfusion injury induced by elevation of intraocular pressure, compound (1 mg/kg i.p.) given before ischemia and immediately after reperfusion significantly prevented ischemia-induced retinal ganglion cell death by 80%. It also inhibited ischemia-induced biochemical changes in the retina such as the increase in lactate content and decrease in glucose. The neuro-protective effect of compound was comparable to that of flunarizine.

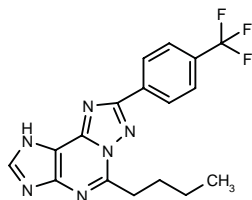
SOURCES – Università degli Studi di Catania, Catania (IT); Università degli Studi di Messina, Messina (IT).

REFERENCES

1. Bucolo, C. et al. *Neuroprotective effect of (-)MR-22, a novel σ_1 receptor ligand, on ischemic injury in the rat retina*. Pharmacologist 2002, 44(2, Suppl. 1): Abst 66.2.
2. Marrazzo, A. et al. *Synthesis and pharmacological evaluation of potent and enantioselective σ_1 and σ_2 ligands*. Farmaco 2001, 56(3): 181.
3. Marrazzo, A. et al. *Synthesis of (+)- and (-)-cis-2-[(1-adamantylamino)-methyl]-1-phenylcyclopropane derivatives as high affinity probes for σ_1 and σ_2 binding sites*. Farmaco 2002, 57(1): 45.
4. Ronsisvalle, G. et al. *Substituted 1-phenyl-2-cyclopropylmethylamines with high affinity and selectivity for sigma sites*. Bioorg Med Chem 2000, 8(6): 1503.

OT-7999***282924**

5-Butyl-8-[4-(trifluoromethyl)phenyl]-1*H*-[1,2,4]triazolo-[5,1-*f*]purine



C17 H15 F3 N6; Mol wt: 360.3415

ACTION – Potent and selective human adenosine A₃ receptor ligand ($K_i = 0.95$ nM) with > 10,500-fold selectivity relative to other adenosine receptor subtypes. In ocular normotensive monkeys, topical application of 500 µg produced significant reductions in intraocular pressure (IOP) at 2-4 h following application; compound was well tolerated in terms of ocular irritation and toxicity. Potentially useful for the treatment of glaucoma.

SOURCE – Otsuka.

REFERENCES

1. Okamura, T. et al. (Otsuka Pharmaceutical Co., Ltd.) *Triazolopurine derivs, medicinal compsn. containing the derivs., adenosine A3 receptor compatibilizing agent, and asthmatic remedy*. EP 1069126, US 6288070, WO 9951606.

2. Okamura, T. et al. *Effect of a novel selective human adenosine A3 receptor ligand, OT-7999, on intraocular pressure in the cynomolgus monkey*. 14th World Congr Pharmacol (July 7-12, San Francisco) 2002, Abst LB 65.

*Identified compound **282924** (see **282915**) Drug Data Rep 2000, 022(01): 0033.

RICIN–MAB 35**321670**

Immunotoxin consisting of ricin conjugated to MAb 35 against nicotinic acetylcholine receptors of skeletal muscle

ACTION – Immunotoxin consisting of ricin linked to a monoclonal antibody that binds the α subunit of the nicotinic acetylcholine receptor in skeletal muscle, able to induce significant and long-lasting muscle loss when injected into rabbit extraocular muscle. The injection of compound into the superior rectus muscle resulted in a focal inflammatory reaction within the muscle accompanied by muscle fiber loss. The immunotoxin did not appear to be acutely toxic to the peripheral nerves. Potentially useful for the treatment of focal muscle dystonias, strabismus or nystagmus.

SOURCE – University of Minnesota, Minneapolis, MN (US).

REFERENCES

1. Christiansen, S.P. et al. *A new candidate immunotoxin for the treatment of strabismus: Ricin-MAB 35*. 3rd Int Symp Ocular Pharmacol Pharm (Feb 10-13, Lisbon) 2000, Abst .

2. Christiansen, S.P. et al. *Acute and chronic effects of the immunotoxin, ricin-MAB 35, in extraocular muscle*. Invest Ophthalmol Visual Sci 2000, 41(4): Abst 2213.

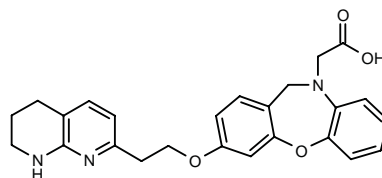
3. Christiansen, S.P. et al. *Acute effects of the skeletal muscle-specific immunotoxin ricin-mAb 35 on extraocular muscles of rabbits*. Invest Ophthalmol Visual Sci 2000, 41(11): 3402.

4. Christiansen, S.P. et al. *Long-term effects of ricin-mAb 35 on extraocular muscles of rabbits: Potential treatment for strabismus*. Invest Ophthalmol Visual Sci 2002, 43(3): 679.

5. Hott, J.S. et al. *Skeletal muscle-specific immunotoxin for the treatment of focal muscle spasm*. Neurology 1998, 50(2): 485.

METABOLIC DRUGS**TREATMENT OF BONE DISEASES****321856**

2-[3-[2-(5,6,7,8-Tetrahydro-1,8-naphthyridin-2-yl)ethoxy]-10,11-dihydrodibenzo[*b,f*][1,4]oxazepin-10-yl]acetic acid



C25 H25 N3 O4; Mol wt: 431.4895

ACTION – Antagonist at $\alpha_v\beta_3$, $\alpha_v\beta_5$ and other α_v integrin receptors associated with β -subunits, potentially useful for the treatment of osteoporosis, as well as restenosis, angiogenesis, diabetic retinopathy, macular degeneration, arthritis and cancer.

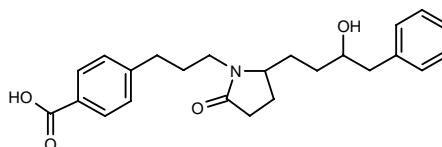
SOURCE – Merck & Co.

REFERENCES

1. Patane, M.A. (Merck & Co., Inc.) *Dibenzoxazepine α V integrin receptor antagonist*. WO 0240505.

322061

4-[3-[2-(3-Hydroxy-4-phenylbutyl)-5-oxopyrrolidin-1-yl]propyl]benzoic acid

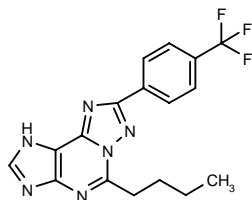


C24 H29 N O4; Mol wt: 395.4961

ACTION – Selective prostaglandin EP₄ receptor agonist with potential utility in the treatment of osteoporosis, frailty, bone defects, childhood idiopathic bone loss, alveolar or mandibular bone loss, bone fracture, osteotomy, bone loss associated with periodontitis and prosthetic ingrowth. Other exemplified compounds include the following:

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SOURCE – Otsuka.

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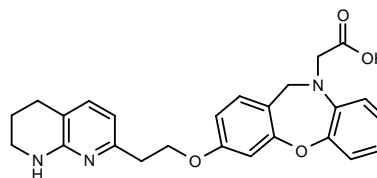
3. Christiansen, S.P. et al. *Acute effects of the skeletal muscle-specific immunotoxin ricin-mAb 35 on extraocular muscles of rabbits*. Invest Ophthalmol Visual Sci 2000, 41(11): 3402.

4. Christiansen, S.P. et al. *Long-term effects of ricin-mAb 35 on extraocular muscles of rabbits: Potential treatment for strabismus*. Invest Ophthalmol Visual Sci 2002, 43(3): 679.

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METABOLIC DRUGS**TREATMENT OF BONE DISEASES****321856**

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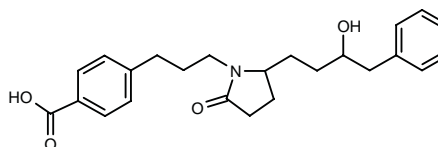
SOURCE – Merck & Co.

REFERENCES

1. Patane, M.A. (Merck & Co., Inc.) *Dibenzoxazepine α V integrin receptor antagonist*. WO 0240505.

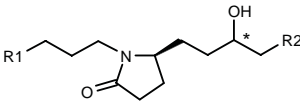
322061

4-[3-[2-(3-Hydroxy-4-phenylbutyl)-5-oxopyrrolidin-1-yl]propyl]benzoic acid

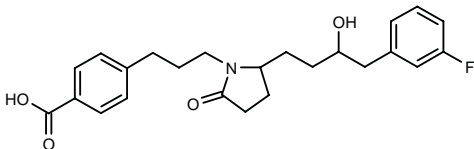


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Compound	R1	R2	*Isomer	Formula
322065	(CH2)3CO2H	3-(MeOCH2)-Ph	R	C ₂₃ H ₃₅ NO ₅
322068	5-CO2H-2-thienyl	2-thienyl		C ₂₀ H ₂₅ NO ₄ S ₂
322069	5-CO2H-2-thienyl	4-F-Ph	R	C ₂₂ H ₂₆ FNO ₄ S
322071	5-CO2H-2-thienyl	3-CF3-Ph	R	C ₂₃ H ₂₆ F ₃ NO ₄ S
322072	5-tetrazolyl-(CH2)3	2-Naph		C ₂₅ H ₃₃ N ₅ O ₂
322074	5-tetrazolyl-(CH2)3	3-(MeOCH2)-Ph	R	C ₂₃ H ₃₅ N ₅ O ₃
322075	4-CO2H-2-thiazolyl	Ph		C ₂₁ H ₂₆ N ₂ O ₄ S



322062: C24 H28 F N O4

SOURCE – Pfizer.

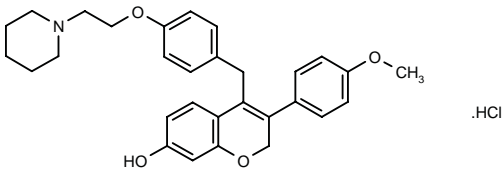
REFERENCES

1. Cameron, K.O. and Lefker, B.A. (Pfizer Products Inc.) *EP4 receptor selective agonists in the treatment of osteoporosis*. WO 0242268.

CHF-4227

312226

3-(4-Methoxyphenyl)-4-[4-[2-(1-piperidinyl)ethoxy]benzyl]-2H-1-benzopyran-7-ol hydrochloride



C30 H33 N O4 . HCl; Mol wt: 508.0546

ACTION – Selective estrogen receptor modulator with high affinity for both human estrogen receptors ER α and ER β (K_i = 0.017 and 0.099 nM, respectively). In immature female rats, compound was more active than raloxifene in inhibiting the uterotrophic effect of 17 α -ethinylestradiol (ED₅₀ = 16 and 390 μ g/kg/day p.o. respectively). In ovariectomized rats, compound completely attenuated the bone loss in the lumbar spine (ED₅₀ = 3 μ g/kg/day p.o.), prevented the increase in serum osteocalcin levels and reduced total serum cholesterol levels (ED₅₀ = 0.33 mg/kg/day p.o.), being 50-100-fold more potent than raloxifene. No uterine stimulant activity was seen in these models. Potentially useful for the treatment or prevention of osteoporosis in postmenopausal women.

SOURCE – Chiesi.

REFERENCES

1. Delcanale, M. et al. (Chiesi Farmaceutici SpA) *2H-1-Benzopyran derivs., processes for their preparation and pharmaceutical compsns. thereof*. WO 0259113.

2. Civelli, M. et al. *CHF 4227.01, a novel benzopyran derivative with improved SERM profile in vivo*. Osteoporosis Int 2002, 13(Suppl. 1): Abst P73MO.

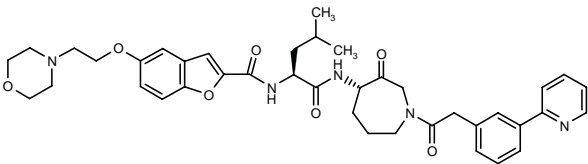
3. Civelli, M. et al. *Effects of CHF 4227, a novel tissue selective estrogen, on bone, serum cholesterol and uterus in rat models*. Pharmacologist 2002, 44(2, Suppl. 1): Abst 96.19.

4. *R&D Pipeline*. Chiesi Group Web Site 2001, Dec 11.

SB-331750*

302659

N-[3-Methyl-1(S)-[N-[3-oxo-1-[2-[3-(2-pyridyl)phenyl]-acetyl]perhydroazepin-4(S)-yl]carbamoyl]butyl]-5-[2-(4-morpholinyl)ethoxy]benzofuran-2-carboxamide



C40 H47 N5 O7; Mol wt: 709.8393

ACTION – Cathepsin K inhibitor (K_i = 0.0048 and 4.7 nmol/l against human and rat enzyme, respectively) with good selectivity over other cathepsins (K_i = 100 nmol/l, 0.48 nmol/l and 14.3 nmol/l, respectively, against cathepsins B, L and S). It also inhibited human osteoclast-associated cathepsin activity (IC₅₀ = 30 nmol/l) and human osteoclast-mediated bone resorption *in vitro* (IC₅₀ = 30 nmol/l). *In vivo* in an acute model of bone resorption in thyroparathyroidectomized rats, compound infused i.v. dose-dependently prevented parathyroid hormone-induced hypercalcemia. In ovariectomized rats, doses of 10 and 30 mg/kg i.p. once daily significantly inhibited the increase in deoxypyridinoline levels, prevented bone turnover and matrix degradation, and exerted beneficial effects on trabecular structure and bone mass, with significant inhibition of ovariectomy-induced loss in bone volume (approximately 60% at 30 mg/kg). Potentially useful for the treatment of disorders characterized by accelerated bone loss such as postmenopausal osteoporosis.

SOURCE – GlaxoSmithKline.

REFERENCES

1. Marquis, R.W. Jr. et al. (GlaxoSmithKline Inc.) *Protease inhibitors*. EP 1158986, WO 0038687.

2. Lark, M.W. et al. *A potent rat cathepsin K inhibitor prevents bone matrix degradation in vivo in the ovariectomized (ovx) rat*. 22nd Annu Meet Am Soc Bone Miner Res (ASBMR) (Sept 22-26, Toronto) 2000, Abst M252.

3. Lark, M.W. et al. *A potent small molecule, nonpeptide inhibitor of cathepsin K (SB 331750) prevents bone matrix resorption in the ovariectomized rat*. Bone 2002, 30(5): 746.

4. Marquis, R.W. et al. *Azepanone-based inhibitors of human and rat cathepsin K*. J Med Chem 2001, 44(9): 1380.

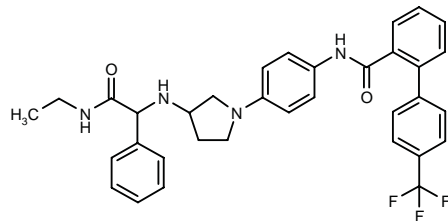
5. Podolin, P.L. et al. *Inhibition of cathepsin S blocks invariant chain processing and antigen-induced proliferation in vitro, and reduces the severity of collagen-induced arthritis in vivo*. Inflamm Res 2001, 50(Suppl. 3): Abst 10/05.

*Identified compound **302659** (see **302658**) Drug Data Rep 2001, 023(07): 0721.

TREATMENT OF LIPOPROTEIN DISORDERS

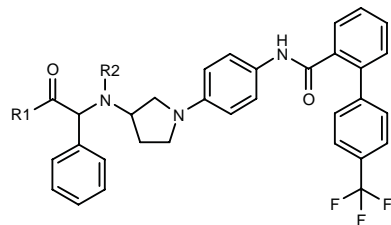
321655

N-[4-[3-[1-(N-Ethylcarbamoyl)-1-phenylmethyl-amino]pyrrolidin-1-yl]phenyl]-4'-(trifluoromethyl)biphenyl-2-carboxamide

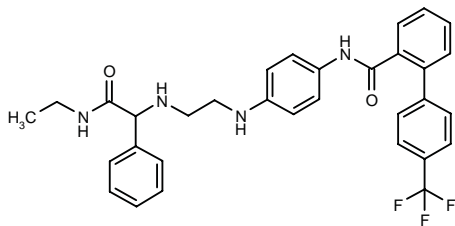


C34 H33 F3 N4 O2; Mol wt: 586.6547

ACTION – Microsomal triglyceride transfer protein (MTP) inhibitor that inhibited the secretion of apolipoprotein B (apo B) in Hep G2 cells with a pIC₅₀ of 7.97. Potentially useful for the treatment of hyperlipidemia, obesity and type 2 diabetes. Other exemplified biphenylcarboxamides are:



Compound	R1	R2	Formula
321657	OMe	Me	C ₃₄ H ₃₂ F ₃ N ₃ O ₃
321658	OMe	H	C ₃₃ H ₃₀ F ₃ N ₃ O ₃
321659	OEt	Me	C ₃₅ H ₃₄ F ₃ N ₃ O ₃
321660	NHEt	Me	C ₃₅ H ₃₅ F ₃ N ₄ O ₂
321661	NHPr	H	C ₃₅ H ₃₅ F ₃ N ₄ O ₂



321656: C32 H31 F3 N4 O2

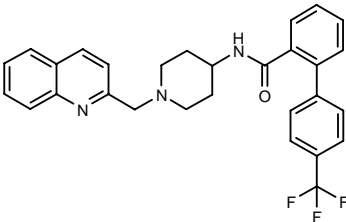
SOURCE – Janssen.

REFERENCES

1. Meerpoel, L. and Backx, L.J. (Janssen Pharmaceutica NV) *Biphenylcarboxamides useful as lipid lowering agents*. WO 0242271.

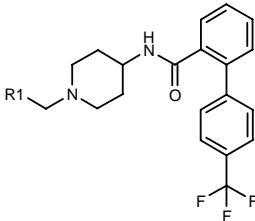
322131

N-[1-(Quinolin-2-ylmethyl)piperidin-4-yl]-4'-(trifluoromethyl)biphenyl-2-carboxamide



C29 H26 F3 N3 O; Mol wt: 489.5384

ACTION – Microsomal triglyceride transfer protein (MTP) inhibitor that gave an IC₅₀ of 26 nM against MTP from hamster liver, and inhibited the secretion of apolipoprotein B (apo B) in Hep G2 cells with an IC₅₀ of 2 nM. Potentially useful for the treatment of hypercholesterolemia, hypertriglyceridemia, hyperlipidemia, pancreatitis, hyperglycemia, obesity, atherosclerosis and dyslipidemia associated with diabetes. Other exemplified piperidine derivatives are:



Compound	R1	Formula
322132	6-Me-2-Pyr	C ₂₆ H ₂₆ F ₃ N ₃ O
322133	2-Me-3-Pyr	C ₂₆ H ₂₆ F ₃ N ₃ O

SOURCE – Merck KGaA.

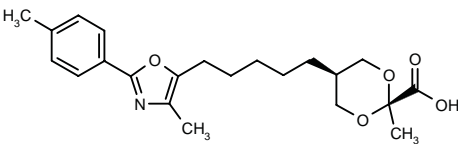
REFERENCES

1. Guevel, A.-C. et al. (Merck Patent GmbH) *4-(Biphenylcarbonylamino)piperidine derivs. as MTP inhibitors*. FR 2816940, WO 0242291.

NS-220

322124

cis-2-Methyl-5-[5-[4-methyl-2-(4-methylphenyl)oxazol-5-yl]pentyl]-1,3-dioxane-2-carboxylic acid



C22 H29 N O5; Mol wt: 387.4731

ACTION – Potent and selective peroxisome proliferator-activated receptor PPAR α agonist (EC_{50} = 10 nM vs. 30 and 100 μ M for PPAR γ and PPAR δ , respectively) able to dose-dependently (0.1-1 mg/kg/day p.o. for 4 days) reduce serum triglyceride levels in diabetic KKA y mice, with a > 80% decrease at the highest dose. In addition, marked increases in HDL cholesterol levels (> 80%) and decreases in non-HDL cholesterol levels were observed following 14 days of treatment at 0.3-1 mg/kg p.o.; no effect on serum triglycerides was seen in PPAR α knockout mice. Potentially useful for the treatment of lipoprotein disorders.

SOURCE – Nippon Shinyaku.

REFERENCES

1. Kuwabara, K. and Aoki, T. (Nippon Shinyaku Co., Ltd.) *Heterocyclic cpds.* WO 0190087.

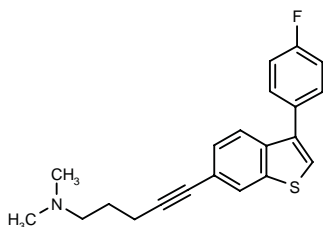
2. Kuwabara, K. et al. *Lipid-lowering effect of a novel dioxane-carboxylic acid derivative, NS-220, a highly selective and potent peroxisome proliferator-activated receptor alpha (PPAR α) agonist.* Pharmacologist 2002, 57(2, Suppl. 1): Abst 93.7.

RO-0721678-000

321332

5-[3-(4-Fluorophenyl)-1-benzothien-6-yl]-*N,N*-dimethyl-4-pentyn-1-amine

N-[5-[3-(4-Fluorophenyl)-1-benzothien-6-yl]-4-pentynyl]-*N,N*-dimethylamine



C21 H20 F N S; Mol wt: 337.4600

ACTION – Cholesterol-lowering agent that inhibits 2,3-epoxysqualene—lanosterol cyclase (lanosterol synthase). Potentially useful for the treatment of disorders associated with elevated cholesterol levels such as hypercholesterolemia, hyperlipidemia, arteriosclerosis, vascular diseases, mycoses, parasitic infections, gallstones, cancer, impaired glucose tolerance and diabetes.

SOURCE – Roche.

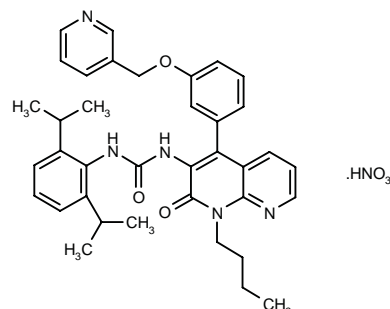
REFERENCES

1. Aebi, J. et al. (F. Hoffmann-La Roche AG) *Cholesterol lowering benzo[b]thiophenes and benzo[d]isothiazoles.* WO 0236584.

SMP-500

321586

N-[1-Butyl-2-oxo-4-[3-(pyridin-3-ylmethoxy)phenyl]-1,2-dihydro-1,8-naphthyridin-3-yl]-*N'*-(2,6-diisopropylphenyl)urea nitrate



C37 H41 N5 O3 . H N O3; Mol wt: 666.7748

ACTION – ACAT inhibitor (IC_{50} = 72 and 84 nM in rabbit liver and small intestine, respectively) able to potently inhibit cholesterol esterification in rat peritoneal macrophages (IC_{50} = 15 nM). In mice fed a high-fat/high-cholesterol diet, compound (3-30 mg/kg/day p.o.) dose-dependently reduced serum total cholesterol levels by 27-46% and non-HDL cholesterol levels by 45-72%, and increased HDL cholesterol levels. The hepatic (total, esterified and free) cholesterol content was also reduced. Compound also showed hypocholesterolemic activity in cholesterol-fed rats (41 and 77% reduction in serum cholesterol at 10-30 mg/kg/day p.o.), rabbits (47-98% reduction in serum total cholesterol at 0.3-10 mg/kg/day p.o.) and in Syrian hamsters (17-40% at 3-30 mg/kg/day p.o.); in these animals a marked reduction in hepatic cholesterol content was also seen. Potentially useful for the treatment of lipoprotein disorders.

SOURCE – Sumitomo Pharmaceuticals.

REFERENCES

1. Muraoka, M. et al. (Sumitomo Pharmaceuticals Co., Ltd.) *Novel naphthyridine derivs.* EP 0947515, JP 1998212288, WO 9823615.

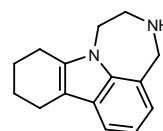
2. Ioriya, K. et al. *Effect of SMP-500, a novel acyl-CoA:cholesterol acyltransferase inhibitor, on the cholesterol esterification and its hypocholesterolemic properties.* Pharmacology 2002, 65(1): 18.

3. Ioriya, K. et al. *Effect of SMP-500, a novel ACAT inhibitor, on hepatic cholesterol disposition in rats.* Lipids 2002, 37(4): 395.

TREATMENT OF OBESITY AND NUTRITIONAL DISORDERS

321235

1,2,3,4,8,9,10,11-Octahydro[1,4]diazepino[6,7,1-*jk*]-carbazole



C15 H18 N2; Mol wt: 226.3212

ACTION – 5-HT_{2C} receptor agonist with a K_i value of 56 nM at 5-HT_{2C} receptors expressed in CHO cells and 90% relative efficacy (5-HT = 100%) for stimulating the production of [³H]-inositol monophosphate. Compound was able to reduce food intake in rats with an ED₅₀ value of 20.86 mg/kg i.p. Potentially useful for the treatment of obsessive–compulsive disorder, depression, anxiety, obesity, eating disorders, migraine, schizophrenia, panic disorders and epilepsy.

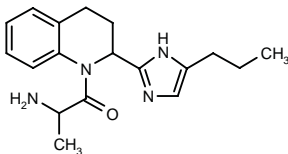
SOURCE – Wyeth.

REFERENCES

1. Sabb, A.L. et al. (Wyeth) *Cycloalkyl[b][1,4]diazepino[6,7,1-h]indoles and derivs.* WO 0236596.

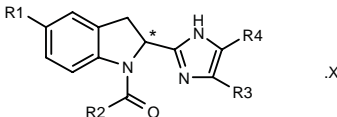
321396

2-Amino-1-[2-(5-propyl-1*H*-imidazol-2-yl)-1,2,3,4-tetrahydroquinolin-1-yl]-1-propanone

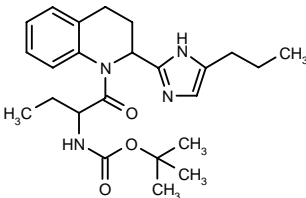


C18 H24 N4 O; Mol wt: 312.4146

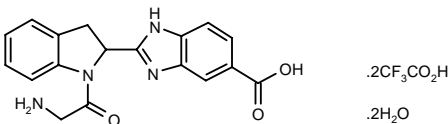
ACTION – An inhibitor of the cholecystokinin-inactivating enzyme tripeptidyl-peptidase II (TPP-II; IC₅₀ < 10 μM), potentially useful for the treatment of eating disorders, obesity, psychosis and psychiatric disorders related therewith. Other exemplified compound are:



Compound	R1	R2	R3	R4	X	*Isomer	Formula
321398	H	2(S)-pyrrolidinyl	H	Pr	2HCl.3H ₂ O	S	C ₁₉ H ₂₄ N ₄ O. 2HCl.3H ₂ O
321400	H	CH ₂ NH ₂	H	CF ₃			C ₁₄ H ₁₃ F ₃ N ₄ O
321401	H	CH ₂ NH ₂	Pr	CO ₂ Et	CF ₃ CO ₂ H		C ₁₉ H ₂₄ N ₄ O ₃ . C ₂ HF ₃ O ₂
321402	OMe	(S)-CH(Me)NH ₂	H	Pr	CF ₃ CO ₂ H	R	C ₁₈ H ₂₄ N ₄ O ₂ . C ₂ HF ₃ O ₂
321403	Cl	(S)-CH(Me)NH ₂	H	Pr	CF ₃ CO ₂ H	R	C ₁₇ H ₂₁ ClN ₄ O. C ₂ HF ₃ O ₂
321404	Cl	(S)-CH(Me)NH ₂	H	Et		R	C ₁₆ H ₁₉ ClN ₄ O



321397: C24 H34 N4 O3



321399: C18 H16 N4 O3 . 2C2 H F3 O2 . 2H2O

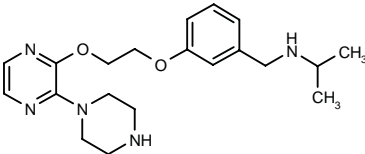
SOURCE – Janssen.

REFERENCES

1. Breslin, H.J. et al. (Janssen Pharmaceutica NV) *Tripeptidyl peptidase inhibitors.* WO 0236116.

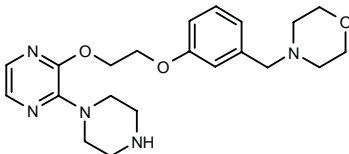
321858

N-Isopropyl-*N*-[3-[2-[3-(1-piperazinyl)pyrazin-2-yloxy]-ethoxy]benzyl]amine



C20 H29 N5 O2; Mol wt: 371.4821

ACTION – 5-HT_{2C} receptor antagonist proven to inhibit [³H]-5-HT binding to 5-HT_{2C} receptors expressed in HEK293 cells with a K_i of 3 nM. Potentially useful for the treatment of obesity and other 5-HT_{2C}-related disorders including memory disorders, schizophrenia, mood disorders, anxiety, pain, drug abuse, sexual dysfunction, epilepsy and urinary disorders. Another exemplified compound is:



321859: C21 H29 N5 O3

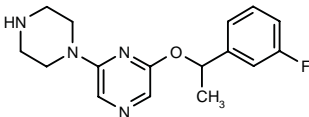
SOURCE – Biovitrum.

REFERENCES

1. Nilsson, B. and Scobie, M. (Biovitrum AB) *Piperazinylpyrazines cpds. as antagonists of serotonin 5-HT₂ receptor.* WO 0240457.

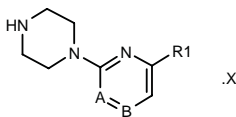
321915

2-[1-(3-Fluorophenyl)ethoxy]-6-(1-piperazinyl)pyrazine

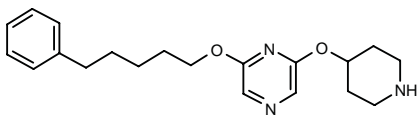


C16 H19 F N4 O; Mol wt: 302.3511

ACTION – Agent with affinity for 5-HT_{2C} receptors (K_i = 8 nM), claimed for use in the treatment of eating disorders, obesity, memory disorders, mood disorders, anxiety, sexual dysfunction, epilepsy, urinary disorders, pain, drug abuse and schizophrenia. Other exemplified piperazinyl-pyrazine compounds are:



Compound	R1	A	B	X	Formula
321916	3-Pyr-CH2CH2O	CH	N	acetate	C ₁₅ H ₁₉ N ₅ O ₂ ·C ₂ H ₄ O ₂
321917	2-furyl	CH	N		C ₁₂ H ₁₄ N ₄ O
321918	2-thienyl-CH2O	CH	CH		C ₁₄ H ₁₇ N ₃ OS
321919	OCH2Ph	CH	N		C ₁₅ H ₁₈ N ₄ O
321920	OCH2CH2F	CH	N	fumarate	C ₁₀ H ₁₅ FN ₄ O ₂ ·C ₄ H ₄ O ₄
321921	OCH2Ph	N	CH	2HCl	C ₁₅ H ₁₈ N ₄ O ₂ ·2HCl



321922: C20 H27 N3 O2

SOURCE – Biovitrum.

REFERENCES

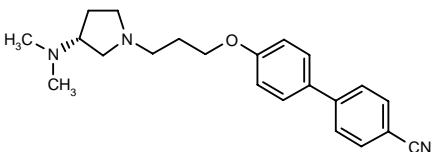
1. Nilsson, B. (Biovitrum AB) *Piperaziny pyrazine cpds. as agonist or antagonist of serotonin 5HT₂ receptor.* WO 0240456.

A-331440

321185

4'-[3-[3(*R*)-(Dimethylamino)pyrrolidin-1-yl]propoxy]-biphenyl-4-carbonitrile

ABBOTT-331440



C22 H27 N3 O; Mol wt: 349.4753

ACTION – Potent and selective histamine H₃ receptor antagonist with high affinity for rat and human H₃ receptors (K_i = 6.3 and 3.6 nM, respectively) and high selectivity over human histamine H₁, H₂ and H₄ receptors (pK_i = 5.53, 4.84 and < 5, respectively). Compound exhibited functional antagonism in several *in vitro* assays, with respective K_b values of 517 and 207 nM in C6 cells expressing human and rat histamine H₃ receptors, and it potently antagonized histamine-mediated histamine release in rat brain cortical synaptosomes (K_b = 44 nM). *In vivo* in a model of high-fat diet-induced obesity in mice, compound (0.5-15 mg/kg p.o. b.i.d.) produced weight loss accompanied by only a moderate decrease in food consumption and by a preferential loss in body fat content. The high dose (15 mg/kg) decreased fat content to levels lower than those observed in mice fed a low-fat diet, improved insulin sensitivity and reduced plasma leptin. Potentially useful for the treatment of obesity.

SOURCE – Abbott.

REFERENCES

1. Bennani, Y.L. et al. (Abbott Laboratories) *1,3-Disubstd. and 1,3,3-trisubstd. pyrrolidines as histamine-3 receptor ligands and their therapeutic applications.* US 2002035103.

2. Bennani, Y.L. et al. (Abbott Laboratories) *1,3-Disubstd. and 1,3,3-trisubstd. pyrrolidines as histamine-3 receptor ligands and their therapeutic applications.* WO 0206223.

3. Bush, E.N. et al. *Histamine H3 receptor antagonist, ABBOTT-331440 normalizes body weight in male C57BL/6J mice with high fat diet-induced obesity.* Diabetes 2002, 51(Suppl. 2): Abst 1715-P.

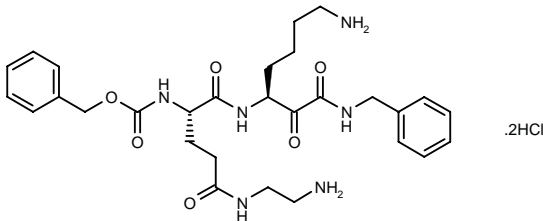
4. Hancock, A.A. et al. *Anti-obesity effects of the non-imidazole histamine H3 receptor antagonist, A-331440.* Pharmacologist 2002, 44(2, Suppl. 1): Abst 96.13.

5. Krueger, K. et al. *Pharmacological properties of the novel histamine H3 receptor antagonist, A-331440.* Pharmacologist 2002, 44(2, Suppl. 1): Abst 110.18.

DENTAL AGENTS

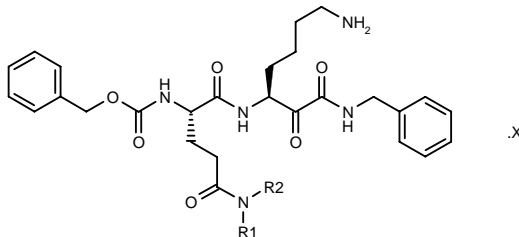
321548

N¹-[5-Amino-1(*S*)-[2-(benzylamino)oxalyl]pentyl]-N⁵-(2-aminoethyl)-N²-(benzyloxycarbonyl)-L-glutaminamide dihydrochloride

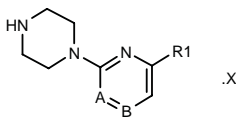


C29 H40 N6 O6 . 2HCl; Mol wt: 641.5928

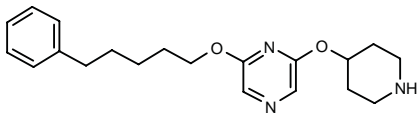
ACTION – A peptide derivative that inhibits Lys-gingipain produced by *Porphyromonas gingivalis*, and is thus potentially useful for the treatment of periodontitis. At a concentration of 1 nM, the compound inhibited Lys-gingipain by 99.9%, while showing no activity against the related enzyme Arg-gingipain. Other exemplified compounds are:



Compound	R1	R2	X	Formula
321550	H	H	HCl	C ₂₇ H ₃₅ N ₅ O ₆ ·HCl
321552	Me	H	HCl	C ₂₈ H ₃₇ N ₅ O ₆ ·HCl
321554	Me	Me	HCl	C ₂₉ H ₃₉ N ₅ O ₆ ·HCl
321555	-CH2CH2NHCH2CH2-		2HCl	C ₃₁ H ₄₂ N ₆ O ₆ ·2HCl
321556	N(Me)2	H	2HCl	C ₂₉ H ₃₉ N ₅ O ₆ ·2HCl
321557	N(Me)Ph	H	2HCl	C ₃₄ H ₄₂ N ₆ O ₆ ·2HCl



Compound	R1	A	B	X	Formula
321916	3-Pyr-CH2CH2O	CH	N	acetate	C ₁₅ H ₁₉ N ₅ O ₂ ·C ₂ H ₄ O ₂
321917	2-furyl	CH	N		C ₁₂ H ₁₄ N ₄ O
321918	2-thienyl-CH2O	CH	CH		C ₁₄ H ₁₇ N ₃ OS
321919	OCH2Ph	CH	N		C ₁₅ H ₁₈ N ₄ O
321920	OCH2CH2F	CH	N	fumarate	C ₁₀ H ₁₅ FN ₄ O ₂ ·C ₄ H ₄ O ₄
321921	OCH2Ph	N	CH	2HCl	C ₁₅ H ₁₈ N ₄ O ₂ ·2HCl



321922: C20 H27 N3 O2

SOURCE – Biovitrum.

REFERENCES

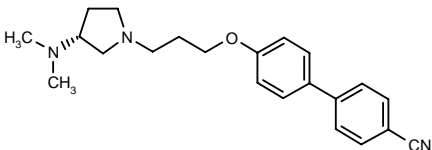
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A-331440

321185

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ABBOTT-331440



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SOURCE – Abbott.

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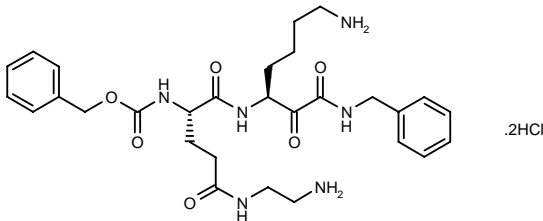
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DENTAL AGENTS

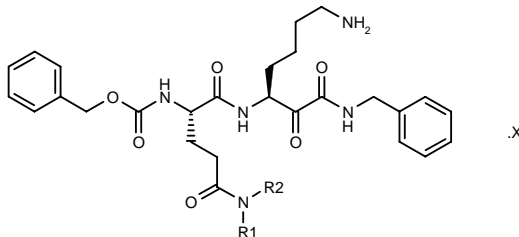
321548

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C29 H40 N6 O6 . 2HCl; Mol wt: 641.5928

ACTION – A peptide derivative that inhibits Lys-gingipain produced by *Porphyromonas gingivalis*, and is thus potentially useful for the treatment of periodontitis. At a concentration of 1 nM, the compound inhibited Lys-gingipain by 99.9%, while showing no activity against the related enzyme Arg-gingipain. Other exemplified compounds are:



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321550	H	H	HCl	C ₂₇ H ₃₅ N ₅ O ₆ ·HCl
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321554	Me	Me	HCl	C ₂₉ H ₃₉ N ₅ O ₆ ·HCl
321555	-CH2CH2NHCH2CH2-		2HCl	C ₃₁ H ₄₂ N ₆ O ₆ ·2HCl
321556	N(Me)2	H	2HCl	C ₂₉ H ₃₉ N ₅ O ₆ ·2HCl
321557	N(Me)Ph	H	2HCl	C ₃₄ H ₄₂ N ₆ O ₆ ·2HCl

SOURCE – Taiho.

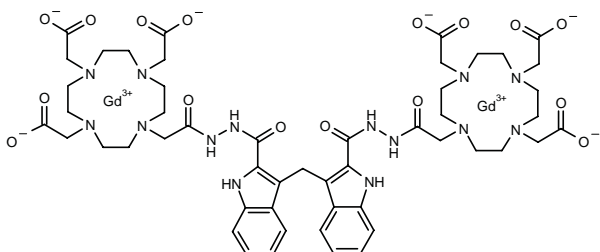
REFERENCES

1. Yamamoto, K. et al. (Taiho Pharmaceutical Co., Ltd.) *Peptide derivs. and their pharmaceutically acceptable salts, processes for preparation of both, and use thereof.* WO 0236551.

DIAGNOSTIC AGENTS

321042

10,10'-(Methylene)bis(1*H*-indol-3,2-diyl)bis(oxomethylene)bis(hydrazo)bis(2-oxoethane-2,1-diyl)bis-[1,4,7,10-tetraazacyclododecane-1,4,7-tris(acetato)(3-)-gadolinium]



C51 H64 Gd2 N14 O16; Mol wt: 1443.6490

ACTION – Contrast agent for the diagnosis of necrotic lesions resulting from ischemic insults. Compound is described as useful for the visualization of the circulatory, hepatobiliary and renal-urinary systems. *In vivo*, i.v. administration of the compound resulted in appropriate visualization of liver infarction in rats, myocardial infarction in pigs and liver metastasis in rats. In addition, it demonstrated good pharmacokinetic properties and low toxicity in rats.

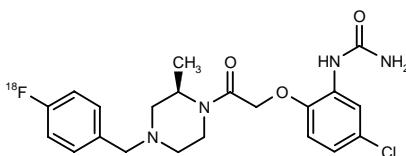
SOURCE – Katholieke Universiteit Leuven, Leuven (BE).

REFERENCES

1. Cresens, E. et al. (Katholieke Universiteit Leuven) *Substd. bis-indole derivs. useful as contrast agents, pharmaceutical compsns. containing them and intermediates for producing them.* WO 0238546.

321228

1-[5-Chloro-2-[2-[4-(4-[¹⁸F]fluorobenzyl)-2(*R*)-methylpiperazin-1-yl]-2-oxoethoxy]phenyl]urea



C21 H24 Cl F N4 O3; Mol wt: 433.8986

ACTION – A representative compound from a series of radiolabeled chemokine CCR1 receptor antagonists with the ability to pass through the blood-brain barrier. A [¹⁴C]-labeled analogue of title compound effectively crossed the blood-brain barrier following i.v. administration to mice at a dose of 36 mg/kg. Potentially useful as an imaging agent in the diagnosis of Alzheimer's disease.

SOURCE – Schering AG.

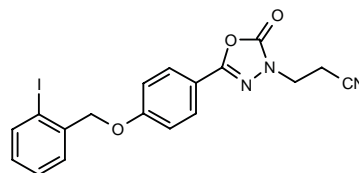
REFERENCES

1. Hilger, C.-S. et al. (Schering AG) *Radiopharmaceuticals for diagnosing Alzheimer's disease.* WO 0236581.

2-IBPO

321772

3-[5-[4-(2-Iodobenzyloxy)phenyl]-2-oxo-1,3,4-oxadiazol-3(2*H*)-yl]propanenitrile



C18 H14 I N3 O3; Mol wt: 447.2266

ACTION – Monoamine oxidase B (MAO-B) inhibitor (IC₅₀ = 2 nM) with more than 50,000-fold selectivity over MAO-A. *In vivo* distribution studies in mice with the iodinated form of compound showed high initial uptake and prolonged retention in the brain and a high brain/blood radioactivity ratio. Potentially useful as a single photon emission computed tomography (SPECT) radiopharmaceutical for functional MAO-B studies in the human brain.

SOURCE – Osaka University, Osaka (JP).

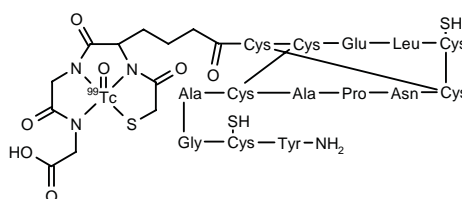
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1. Hirata, M. et al. *Synthesis and characterization of radioiodinated MD-230254: A new ligand for potential imaging of monoamine oxidase B activity by single photon emission computed tomography.* Chem Pharm Bull 2002, 50(5): 609.

^{99m}Tc-NC-100586

320905

[*N*-[5-[*N*-[*N*-(Carboxymethyl)carbamoylmethyl]carbamoyl]-5-(2-sulfanylacetamido)pentanoyl]-L-cysteinyl-L-cysteinyl-L-glutamyl-L-leucyl-L-cysteinyl-L-cysteinyl-L-asparaginyl-L-prolyl-L-alanyl-L-cysteinyl-L-alanyl-glycyl-L-cysteinyl-L-tyrosinamide S-3.1-S-3.6:S-3.2-S-3.10-bis(disulfide)] oxotechnetium-^{99m}Tc



C67 H95 N19 O25 S7 Tc; Mol wt: 1890.0570

SOURCE – Taiho.

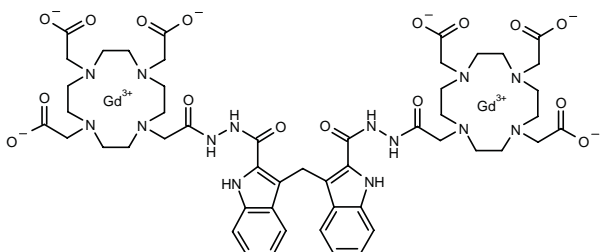
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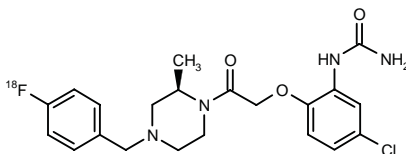
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SOURCE – Schering AG.

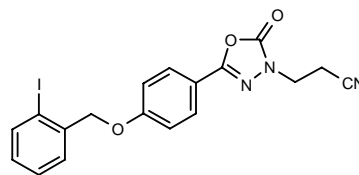
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2-IBPO

321772

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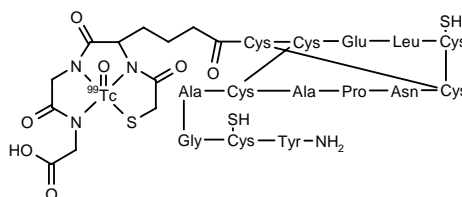
REFERENCES

1. Hirata, M. et al. *Synthesis and characterization of radioiodinated MD-230254: A new ligand for potential imaging of monoamine oxidase B activity by single photon emission computed tomography.* Chem Pharm Bull 2002, 50(5): 609.

^{99m}Tc-NC-100586

320905

[*N*-[5-[*N*-[*N*-(Carboxymethyl)carbamoylmethyl]carbamoyl]-5-(2-sulfanylaceto)pentanoyl]-L-cysteinyl-L-cysteinyl-L-glutamyl-L-leucyl-L-cysteinyl-L-cysteinyl-L-asparaginyl-L-prolyl-L-alanyl-L-cysteinyl-L-alanyl-glycyl-L-cysteinyl-L-tyrosinamide S-3.1-S-3.6:S-3.2-S-3.10-bis(disulfide)] oxotechnetium-^{99m}Tc



C67 H95 N19 O25 S7 Tc; Mol wt: 1890.0570

ACTION – Imaging agent, an analogue of *Escherichia coli* heat-stable enterotoxin (STa) that selectively binds with subnanomolar affinity to the extracellular domain of guanylyl cyclase C, a transmembrane receptor selectively expressed in human intestinal cells and primary and metastatic colorectal adenocarcinomas. In mice bearing human colon cancer xenografts, the radiolabeled compound exhibited selective uptake into tumor xenografts expressing guanylyl cyclase C, as well as hepatic metastases, but not in normal tissues or other tumors not expressing the receptor. Potentially useful as imaging agent with high specificity for metastatic colorectal tumors, as well as for the delivery of therapeutics to colorectal tumors and metastases.

SOURCES – Amersham Health; Targeted Diagnostics & Therapeutics.

REFERENCES

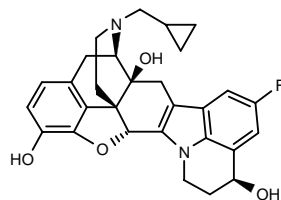
1. Wolfe, H.R. et al. *In vivo imaging of human colon cancer xenografts in immunodeficient mice using a guanylyl cyclase C-specific ligand*. J Nucl Med 2002, 43(3): 392.
-

**ANALGESIC AND ANESTHETIC
DRUGS**

ANALGESIC DRUGS

322445

(4b*S*,8*R*,8a*S*,13*S*,16b*R*)-7-(Cyclopropylmethyl)-11-fluoro-5,6,7,8,9,14,15,16b-octahydro-4,8-methano-8a*H*,13*H*-benzofuro[2,3-*a*]dipyrido[4,3-*b*:3',2',1'-*jk*]carbazole-1,8a,13-triol



C29 H29 F N2 O4; Mol wt: 488.5561

ACTION – Agent with affinity for delta opioid receptors, giving a pA_2 value of 8.4 in functional studies using electrically stimulated mouse vas deferens preparations. Potentially useful as an analgesic, antitussive, immunosuppressant and neuroprotective agent, and expected to be devoid of side effects such as dependency, constipation and respiratory depression by virtue of its selectivity.

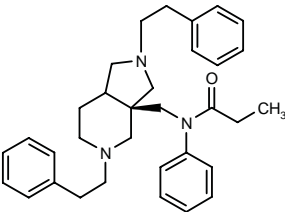
SOURCE – Toray.

REFERENCES

1. Sakami, S. et al. (Toray Industries, Inc.) *Indole derivs. and use thereof in medicines*. WO 0242309.

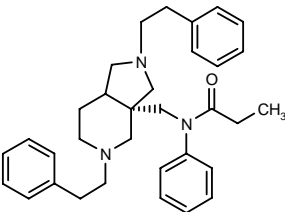
322700

N-[2,5-Bis(2-phenylethyl)perhydropyrrolo[3,4-*c*]pyridin-3a(*R*)-ylmethyl]-*N*-phenylpropionamide



C33 H41 N3 O; Mol wt: 495.7069

ACTION – Agent with affinity for opioid and other G-protein-coupled membrane receptors (GPCRs), potentially useful as an analgesic agent, and also for the treatment of drug abuse and tinnitus. This compound was able to bind to human opioid receptors in radioligand binding assays, and displayed ED_{50} values of 0.05 and 0.06 mg/kg, respectively, in the tail-flick and hot-plate tests. Another exemplified diazabicyclo[4.3.0]nonane is:



322701: C33 H41 N3 O

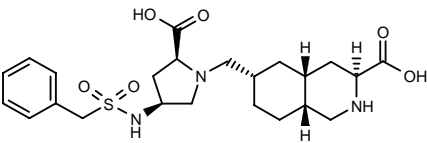
SOURCE – Sepracor.

REFERENCES

1. Wu, X. (Sepracor Inc.) *Analgesic diazabicyclo[4.3.0]nonanes*. WO 0246187.

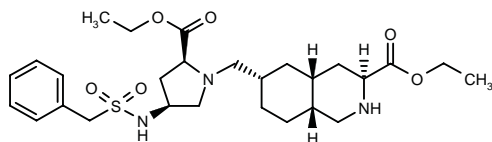
324232

(3*S*,4a*R*,6*S*,8a*R*)-6-[4(*S*)-(Benzylsulfonamido)-2(*S*)-carboxypyrrolidin-1-ylmethyl]perhydroisoquinoline-3-carboxylic acid



C23 H33 N3 O6 S; Mol wt: 479.5947

ACTION – Excitatory amino acid receptor antagonist, particularly inotropic glutamate GluR5 receptor antagonist. Potentially useful for the treatment of neurological and neurodegenerative disorders, particularly pain and migraine. Another specifically claimed compound is:



324233: C27 H41 N3 O6 S

SOURCE – Lilly.

REFERENCES

1. Bleisch, T.J. et al. (Eli Lilly and Company) *Excitatory amino acid receptor antagonists*. WO 0253556.

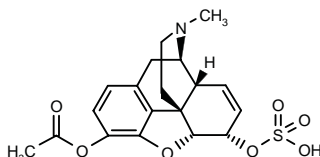
M3A6S

322689

Sulfuric acid (4*R*,4*aR*,7*aR*,12*bS*)-9-acetoxy-3-methyl-2,3,4,4*a*,7,7*a*-hexahydro-1*H*-4,12-methano[1]benzofuro[3,2-*e*]isoquinolin-7-yl monoester

Sulfuric acid 3-*O*-acetyl-7,8-didehydro-4,5*α*-epoxy-17-methylmorphinan-6*α*-yl monoester

3-*O*-Acetylmorphine-6-*O*-sulfate



C19 H21 N O7 S; Mol wt: 407.4409

ACTION – Analgesic agent, an analogue of morphine-6-sulfate shown to act selectively at mu and kappa opioid receptors. Compound demonstrated *in vivo* activity in the tail-flick test following either s.c. or intracerebroventricular (i.c.v.) administration. In morphine withdrawal studies in morphine-dependent rhesus monkeys, it did not substitute for morphine nor exacerbate withdrawal, suggesting absence of mu opioid-like activity in this model.

SOURCE – University of Kentucky, Lexington, KY (US).

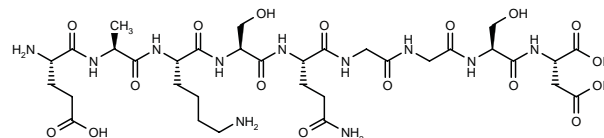
REFERENCES

1. Crooks, P.A. et al. (University of Kentucky) *Morphine-6-sulfate analogues and their use for the treatment of pain*. US 6403602.

PAT

322493

L-Glutamyl-L-alanyl-L-lysyl-L-seryl-L-glutamyl-glycyl-glycyl-L-seryl-L-aspartic acid



C33 H55 N11 O17; Mol wt: 877.8575

ACTION – Synthetic peptide analogue of thymulin with potent analgesic and antiinflammatory activity. In two rat models of peripheral mononeuropathy involving chronic constriction injury of the sciatic nerve or spared nerve injury, compound (0.25-25 mg i.p.) dose-dependently reduced mechanical allodynia and heat hyperalgesia, with a peak effect at 1-2 h after dosing that persisted for up to 4 h. In these models, it was more effective than meloxicam or morphine. In rat models of inflammatory hyperalgesia induced by intraplantar or i.p. injection of endotoxin, compound (1-25 µg i.p.) dose-dependently decreased mechanical and thermal hyperalgesia and was at least as active as other antiinflammatory drugs including dexamethasone and indomethacin. The antihyperalgesic and antiinflammatory effects of compound appeared to be due, at least in part, to downregulation of proinflammatory mediators.

SOURCES – American University of Beirut, Beirut (LB); CNRS.

REFERENCES

1. Pleau, J.M. et al. *Antagonistic analog of serum thymic factor (FTS) interacting with the FTS cellular receptor*. Immunol Lett 1979, 1(3): 179.

2. Saade, N.E. et al. *Attenuation of neuropathic manifestations in rats by a synthetic peptide analogue of thymulin (PAT)*. 3rd Forum Eur Neurosci (July 13-17, Paris) 2002, Abst 183.18.

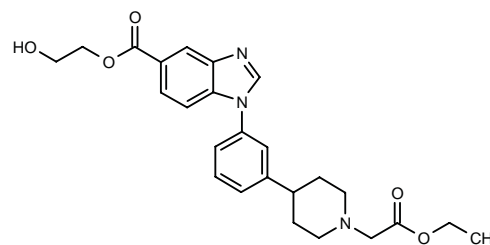
3. Safieh-Garabedian, B. et al. *Potent analgesic and anti-inflammatory actions of a novel thymulin-related peptide in the rat*. Br J Pharmacol 2002, 136(6): 947.

4. Safieh-Garabedian, B. et al. *Prevention of ET-induced hyperalgesia in the rat, by a novel thymulin peptide analogue (PAT)*. 3rd Forum Eur Neurosci (July 13-17, Paris) 2002, Abst 183.19.

ANESTHETIC DRUGS

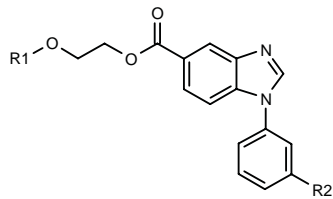
323502

1-[3-[1-(Ethoxycarbonylmethyl)piperidin-4-yl]phenyl]-1*H*-benzimidazole-5-carboxylic acid 2-hydroxyethyl ester



C25 H29 N3 O5; Mol wt: 451.5201

ACTION – Modulator of GABA_A receptors with potential as an anesthetic, muscle relaxant and sedative, as well as in the prevention and treatment of febrile convulsions. Other specifically claimed benzimidazole derivatives are:



Compound	R1	R2	Formula
323503	Me	1-(EtOCOCH2)-4-Pip	C ₂₆ H ₃₁ N ₅ O ₅
323505	H	1-(MeOCOCH2)-4-Pip	C ₂₄ H ₂₇ N ₅ O ₅
323506	Me	1-(MeOCOCH2)-4-Pip	C ₂₅ H ₂₉ N ₅ O ₅
323508	Me	4-[N(Et)2COCH2]-perhydro-1,4-diazepin-1-yl	C ₂₈ H ₃₇ N ₅ O ₄
323509	H	1-[N(Et)2COCH2]-4-Pip	C ₂₇ H ₃₄ N ₄ O ₄
323510	Me	1-[N(Et)2COCH2]-4-Pip	C ₂₈ H ₃₆ N ₄ O ₄
323512	Me	4-[N(Me)2COCH2]-1-Piz	C ₂₅ H ₃₁ N ₅ O ₄
323513	Me	4-[N(Me)2COCH2]-perhydro-1,4-diazepin-1-yl	C ₂₆ H ₃₃ N ₆ O ₄

SOURCE – NeuroSearch.

REFERENCES

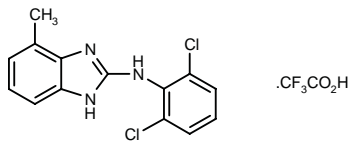
1. Teuber, L. and Wätjen, F. (NeuroSearch A/S) *Novel benzimidazole derivs. for the treatment of GABA-alfa mediated disorders*. WO 0250057.

PSYCHOPHARMACOLOGIC DRUGS

TREATMENT OF SLEEP DISORDERS

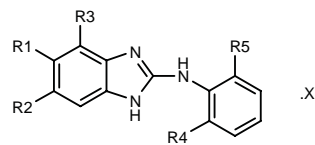
322786

N-(2,6-Dichlorophenyl)-4-methyl-1*H*-benzimidazol-2-amine trifluoroacetate



C14 H11 Cl2 N3 . C2 H F3 O2; Mol wt: 406.1898

ACTION – An inhibitor of the Na⁺/H⁺ exchanger subtype 3 (NHE3; IC₅₀ = 0.39 μM) reported to be useful for the treatment of sleep apnea, acute and chronic renal failure, intestinal and biliary disorders, stroke, peripheral ischemic disorders, shock, proliferative disorders, lipid metabolism disorders and ectoparasitic infections, as well as for the preservation of organs for transplantation. Other exemplified 2-anilinobenzimidazoles are:



Compound	R1	R2	R3	R4	R5	X	Formula
322787	H	H	H	Cl	Cl	HCl	C ₁₃ H ₉ Cl ₂ N ₃ .HCl
322788	H	H	OH	Cl	Cl	HCl	C ₁₃ H ₉ Cl ₂ N ₃ O.HCl
322789	H	H	H	Me	Me	CF3CO2H	C ₁₅ H ₁₅ N ₃ .C ₂ HF ₃ O ₂
322790	H	H	H	Me	Cl	HCl	C ₁₄ H ₁₂ ClN ₃ .HCl
322791	F	F	H	Cl	Cl	HCl	C ₁₃ H ₇ Cl ₂ F ₂ N ₃ .HCl
322792	H	H	H	F	Cl	HCl	C ₁₃ H ₉ ClFN ₃ .HCl
322793	H	H	H	Br	Br	CF3CO2H	C ₁₃ H ₉ Br ₂ N ₃ .C ₂ HF ₃ O ₂
322794	H	H	H	CF3	Cl	HCl	C ₁₄ H ₉ ClF ₃ N ₃ .HCl
322795	H	H	H	Cl	H	CF3CO2H	C ₁₃ H ₁₀ ClN ₃ .C ₂ HF ₃ O ₂

SOURCE – Aventis Pharma.

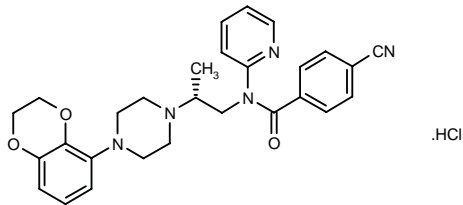
REFERENCES

1. Hofmeister, A. et al. (Aventis Pharma Deutschland GmbH) *Substd. 2-anilino-benzimidazoles and the use thereof as NHE-inhibitors*. DE 10060292, WO 0246169.

ANXIOLYTICS

322323

4-Cyano-*N*-[2(*R*)-[4-(2,3-dihydro-1,4-benzodioxin-5-yl)-piperazin-1-yl]propyl]-*N*-(2-pyridyl)benzamide hydrochloride



C28 H29 N5 O3 . HCl; Mol wt: 520.0300

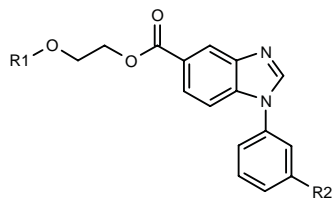
ACTION – 5-HT_{1A} receptor antagonist with high affinity for the receptor in a binding assay (K_i = 1.6 nM) and antagonist activity in functional assays (IC₅₀ = 25 nM). In the rat fixed-responding model, compound completely antagonized the effects of the 5-HT_{1A} agonist 8-OH-DPAT at a dose of 1 mg/kg s.c., exhibiting a duration of action of over 4 h. Potentially useful for the treatment of anxiety, depression, schizophrenia, cognitive disorders, drug abuse, Parkinson's disease, migraine, eating disorders, sexual dysfunction, urinary incontinence, stroke, endocrine disorders, sleep disorders, attention deficit disorders, Tourette's syndrome, autism, social phobias, hyperactivity disorders and thermoregulatory disorders.

SOURCE – Wyeth.

REFERENCES

1. Childers, W.E. et al. (Wyeth) *Serotonergic agents*. WO 0244142.

ACTION – Modulator of GABA_A receptors with potential as an anesthetic, muscle relaxant and sedative, as well as in the prevention and treatment of febrile convulsions. Other specifically claimed benzimidazole derivatives are:



Compound	R1	R2	Formula
323503	Me	1-(EtOCOCH2)-4-Pip	C ₂₆ H ₃₁ N ₅ O ₅
323505	H	1-(MeOCOCH2)-4-Pip	C ₂₄ H ₂₇ N ₅ O ₅
323506	Me	1-(MeOCOCH2)-4-Pip	C ₂₅ H ₂₉ N ₅ O ₅
323508	Me	4-[N(Et)2COCH2]-perhydro-1,4-diazepin-1-yl	C ₂₈ H ₃₇ N ₅ O ₄
323509	H	1-[N(Et)2COCH2]-4-Pip	C ₂₇ H ₃₄ N ₄ O ₄
323510	Me	1-[N(Et)2COCH2]-4-Pip	C ₂₈ H ₃₆ N ₄ O ₄
323512	Me	4-[N(Me)2COCH2]-1-Piz	C ₂₅ H ₃₁ N ₅ O ₄
323513	Me	4-[N(Me)2COCH2]-perhydro-1,4-diazepin-1-yl	C ₂₆ H ₃₃ N ₆ O ₄

SOURCE – NeuroSearch.

REFERENCES

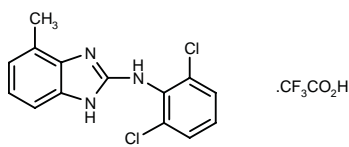
1. Teuber, L. and Wätjen, F. (NeuroSearch A/S) *Novel benzimidazole derivs. for the treatment of GABA-alfa mediated disorders*. WO 0250057.

PSYCHOPHARMACOLOGIC DRUGS

TREATMENT OF SLEEP DISORDERS

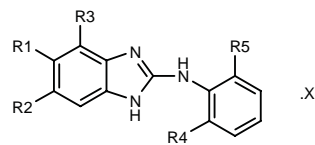
322786

N-(2,6-Dichlorophenyl)-4-methyl-1*H*-benzimidazol-2-amine trifluoroacetate



C14 H11 Cl2 N3 . C2 H F3 O2; Mol wt: 406.1898

ACTION – An inhibitor of the Na⁺/H⁺ exchanger subtype 3 (NHE3; IC₅₀ = 0.39 μM) reported to be useful for the treatment of sleep apnea, acute and chronic renal failure, intestinal and biliary disorders, stroke, peripheral ischemic disorders, shock, proliferative disorders, lipid metabolism disorders and ectoparasitic infections, as well as for the preservation of organs for transplantation. Other exemplified 2-anilinobenzimidazoles are:



Compound	R1	R2	R3	R4	R5	X	Formula
322787	H	H	H	Cl	Cl	HCl	C ₁₃ H ₉ Cl ₂ N ₃ .HCl
322788	H	H	OH	Cl	Cl	HCl	C ₁₃ H ₉ Cl ₂ N ₃ O.HCl
322789	H	H	H	Me	Me	CF3CO2H	C ₁₅ H ₁₅ N ₃ .C ₂ HF ₃ O ₂
322790	H	H	H	Me	Cl	HCl	C ₁₄ H ₁₂ ClN ₃ .HCl
322791	F	F	H	Cl	Cl	HCl	C ₁₃ H ₇ Cl ₂ F ₂ N ₃ .HCl
322792	H	H	H	F	Cl	HCl	C ₁₃ H ₉ ClFN ₃ .HCl
322793	H	H	H	Br	Br	CF3CO2H	C ₁₃ H ₉ Br ₂ N ₃ .C ₂ HF ₃ O ₂
322794	H	H	H	CF3	Cl	HCl	C ₁₄ H ₉ ClF ₃ N ₃ .HCl
322795	H	H	H	Cl	H	CF3CO2H	C ₁₃ H ₁₀ ClN ₃ .C ₂ HF ₃ O ₂

SOURCE – Aventis Pharma.

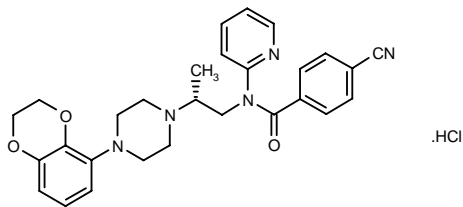
REFERENCES

1. Hofmeister, A. et al. (Aventis Pharma Deutschland GmbH) *Substd. 2-anilino-benzimidazoles and the use thereof as NHE-inhibitors*. DE 10060292, WO 0246169.

ANXIOLYTICS

322323

4-Cyano-*N*-[2(*R*)-[4-(2,3-dihydro-1,4-benzodioxin-5-yl)-piperazin-1-yl]propyl]-*N*-(2-pyridyl)benzamide hydrochloride



C28 H29 N5 O3 . HCl; Mol wt: 520.0300

ACTION – 5-HT_{1A} receptor antagonist with high affinity for the receptor in a binding assay (K_i = 1.6 nM) and antagonist activity in functional assays (IC₅₀ = 25 nM). In the rat fixed-responding model, compound completely antagonized the effects of the 5-HT_{1A} agonist 8-OH-DPAT at a dose of 1 mg/kg s.c., exhibiting a duration of action of over 4 h. Potentially useful for the treatment of anxiety, depression, schizophrenia, cognitive disorders, drug abuse, Parkinson's disease, migraine, eating disorders, sexual dysfunction, urinary incontinence, stroke, endocrine disorders, sleep disorders, attention deficit disorders, Tourette's syndrome, autism, social phobias, hyperactivity disorders and thermoregulatory disorders.

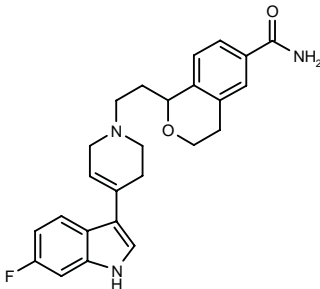
SOURCE – Wyeth.

REFERENCES

1. Childers, W.E. et al. (Wyeth) *Serotonergic agents*. WO 0244142.

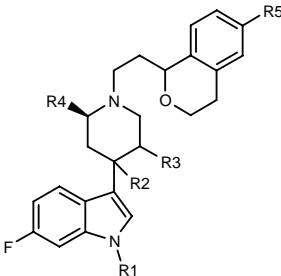
323540

1-[2-[4-(6-Fluoro-1*H*-indol-3-yl)-1,2,3,6-tetrahydropyridin-1-yl]ethyl]-3,4-dihydro-1*H*-2-benzopyran-6-carboxamide

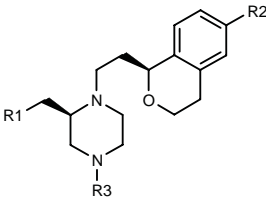


C25 H26 F N3 O2; Mol wt: 419.4974

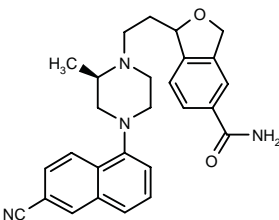
ACTION – 5-HT reuptake inhibitor potentially useful for the treatment of CNS disorders, particularly anxiety and depression. Other applications include bipolar disorder, obesity, eating disorders, alcoholism, pain, hypertension, memory loss, sexual dysfunction, schizophrenia, gastro-intestinal and cardiovascular disorders, epilepsy, drug abuse, smoking cessation, emesis, Alzheimer’s disease and sleep disorders. Other exemplified compounds are:



Compound	R1	R2	R3	R4	R5	Isomer	Formula
323541	H	bond	H	H	Br		C ₂₄ H ₂₄ BrFN ₂ O
323542	H	H	H	Me	CONH2	2R,4S	C ₂₆ H ₃₀ FN ₃ O ₂
323543	Me	bond	H	H	CONH2		C ₂₆ H ₂₈ FN ₃ O ₂



Compound	R1	R2	R3	Formula
323544	H	CONH2	4-CN-6-F-1-Naph	C ₂₈ H ₂₉ FN ₄ O ₂
323545	Me	CONH2	6-CN-3-benzothieryl	C ₂₇ H ₃₀ N ₄ O ₂ S
323546	H	CONH2	2-CN-7-benzothieryl	C ₂₆ H ₂₈ N ₄ O ₂ S
323547	H	3-Pyr	6-CN-1-Naph	C ₃₂ H ₃₂ N ₄ O



323548: C27 H28 N4 O2

SOURCE – Lilly.

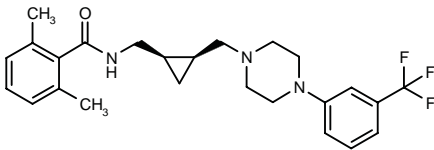
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1. Agejas-Chicharro, J. et al. (Eli Lilly and Company) *Pharmaceutical cpds.* WO 0250067.

ANTIPSYCHOTIC DRUGS

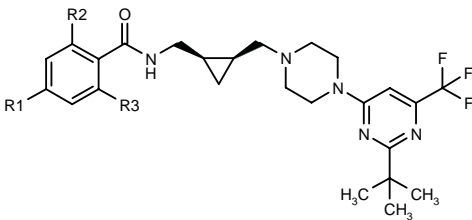
322441

cis-2,6-Dimethyl-*N*-[2-[4-[3-(trifluoromethyl)phenyl]-piperazin-1-ylmethyl]cyclopropylmethyl]benzamide isomer A

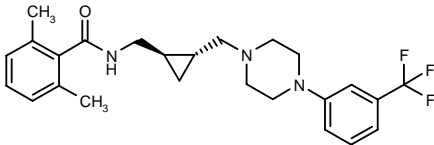


C25 H30 F3 N3 O; Mol wt: 445.5260

ACTION – Dopamine D3 receptor modulator that gave a K_i of 5 nM at D3 receptors expressed in CHO cells and exhibited 92-fold selectivity over D2 receptors. Potentially useful for the treatment of psychosis, anxiety, mood disorders, Parkinson’s disease, hypertension, hypotension, urinary incontinence, drug abuse, sexual dysfunction and movement disorders. Other exemplified acylamino cyclopropane derivatives are:



Compound	R1	R2=R3	Formula
322442	H	Me	C ₂₇ H ₃₆ F ₃ N ₅ O
322444	Cl	H	C ₂₈ H ₃₁ ClF ₃ N ₅ O



322443: C25 H30 F3 N3 O

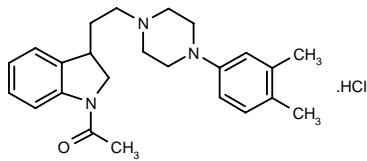
SOURCE – Pfizer.

REFERENCES

1. Fliri, A.F.J. and Reinhold, A.R. (Pfizer Products Inc.) *Acylamino cyclopropane derivs.* EP 1211247, JP 2002205987.

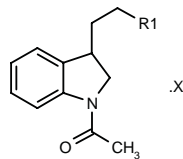
323712

(+)-1-[3-[2-[4-(3,4-Dimethylphenyl)piperazin-1-yl]ethyl]-2,3-dihydro-1*H*-indol-1-yl]ethanone hydrochloride



C24 H31 N3 O . HCl; Mol wt: 413.9898

ACTION – Dual dopamine D4 and 5-HT_{2A} receptor antagonist found to inhibit the binding of [³H]-YM-09151-2 to D4 receptors and the binding of [³H]-ketanserin to 5-HT_{2A} receptors with IC₅₀ values in the nanomolar range. Potentially useful for the treatment of psychiatric and neurological disorders, particularly psychosis. Other exemplified 3-indoline derivatives are:



Compound	R1	X	Isomer	Formula
323713	4-(4-Me-Ph)-1-Piz	HCl	(+)	C ₂₃ H ₂₉ N ₃ O.HCl
323714	4-(4-Me-Ph)-1-Pip		(+)	C ₂₄ H ₃₀ N ₂ O
323715	4-[3,4-(Cl)2-Ph]-1-Piz	HCl	(+)	C ₂₂ H ₂₅ Cl ₂ N ₃ O.HCl
323716	4-(4-Br-Ph)-1-Piz	HCl	(+)	C ₂₂ H ₂₆ BrN ₃ O.HCl
323717	4-[3,4-(Cl)2-Ph]-1,2,3,6-tetrahydro-1-Pyr	HCl		C ₂₃ H ₂₄ Cl ₂ N ₂ O.HCl
323718	4-[3,4-(Cl)2-Ph]-1-Pip	HCl		C ₂₃ H ₂₆ Cl ₂ N ₂ O.HCl

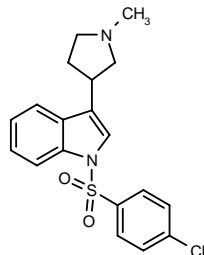
SOURCE – Lundbeck.

REFERENCES

1. Kehler, J. and Bang-Andersen, B. (H. Lundbeck A/S) *3-Indoline derivs. useful in the treatment of psychiatric and neurologic disorders*. WO 0251833.

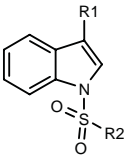
323720

1-(4-Chlorophenylsulfonyl)-3-(1-methylpyrrolidin-3-yl)-1*H*-indole



C19 H19 Cl N2 O2 S; Mol wt: 374.8901

ACTION – Agent with 5-HT₆ binding affinity (K_i = 1 nM), potentially useful for the treatment of a variety of central nervous system disorders and particularly claimed for the treatment of schizophrenia, anxiety, depression, memory loss and attention deficit disorder. Other exemplified indazole compounds include the following:



Compound	R1	R2	Formula
323721	1-Me-3-pyrrolidinyl	4-F-Ph	C ₁₉ H ₁₉ FN ₂ O ₂ S
323722	1-Me-3-pyrrolidinyl	2-Naph	C ₂₃ H ₂₂ N ₂ O ₂ S
323723	1-Me-3-pyrrolidinyl	4-NH2-Ph	C ₁₉ H ₂₁ N ₃ O ₂ S
323724	1-Me-3-pyrrolidinyl	3,4-(MeO)2-Ph	C ₂₇ H ₂₄ N ₂ O ₄ S
323725	1-Me-3-pyrrolidinyl	3,4-(Cl)2-Ph	C ₁₉ H ₁₆ Cl ₂ N ₂ O ₂ S
323726	1-Me-3-pyrrolidinyl	4,5-(Cl)2-2-thienyl	C ₁₇ H ₁₆ Cl ₂ N ₂ O ₂ S ₂
323727	1-Me-3-pyrrolidinyl	2-Br-Ph	C ₁₉ H ₁₈ BrN ₂ O ₂ S
323728	1-Me-3-pyrrolidinyl	4-I-Ph	C ₁₉ H ₁₉ IN ₂ O ₂ S
323729	1-Me-3-pyrrolidinyl	2-I-Ph	C ₁₉ H ₁₉ IN ₂ O ₂ S
323730	1-(PhCH2)-3-pyrrolidinyl	4-NH2-Ph	C ₂₅ H ₂₅ N ₃ O ₂ S
323731	3-Pip	Ph	C ₁₉ H ₂₀ N ₂ O ₂ S
323732	3-Pip	3-Cl-Ph	C ₁₉ H ₁₉ ClN ₂ O ₂ S

SOURCE – Wyeth.

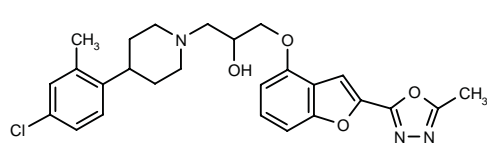
REFERENCES

1. Zhou, P. et al. (American Home Products Corp.) *Heterocyclindazole and azaindazole cpds. as 5-hydroxy-tryptamine-6 ligands*. WO 0251837.

TREATMENT OF MOOD DISORDERS

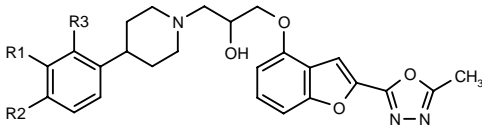
322564

1-[4-(4-Chloro-2-methylphenyl)piperidin-1-yl]-3-[2-(5-methyl-1,3,4-oxadiazol-2-yl)-1-benzofuran-4-yloxy]-propan-2-ol



C26 H28 Cl N3 O4; Mol wt: 481.9772

ACTION – Dual-acting compound that inhibits 5-HT reuptake and antagonizes 5-HT_{1A} receptors, as demonstrated by K_i values for inhibition of [³H]-8-OH-DPAT binding to 5-HT_{1A} receptors and [³H]-paroxetine binding to the 5-HT transporter of 3.8 and 3.0 nM, respectively. In electrophysiological assays using rat brain cells, compounds of the invention were shown to inhibit 8-OH-DPAT-induced K⁺ inward currents, suggesting 5-HT_{1A}-antagonist activity. This was also confirmed *in vivo*, as oral administration of compounds to mice prevented the 8-OH-DPAT-stimulated decrease in body temperature. Title compound demonstrated stability to degradation by rat, monkey and human liver microsomes. Potentially useful for the treatment of depression, schizophrenia, anxiety, panic disorder, eating disorders, traumatic stress disease, senile dementia, migraine, stroke, Alzheimer's disease, hypertension, pain, drug abuse, and also gastrointestinal, thermoregulatory, sexual and cardiovascular disorders. Other exemplified piperidine compounds are:



Compound	R1	R2	R3	Formula
322565	Cl	OEt	H	C ₂₇ H ₃₀ ClN ₃ O ₅
322566	H	OMe	Me	C ₂₇ H ₃₁ N ₃ O ₅
322567	Me	Cl	F	C ₂₆ H ₂₇ ClFN ₃ O ₄
322568	H	SMe	H	C ₂₆ H ₂₈ N ₃ O ₄ S

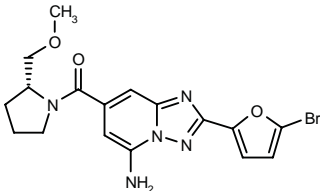
SOURCE – Mitsubishi Pharma.

REFERENCES

1. Nishiyama, A. et al. (Mitsubishi Pharma Corp.) *Piperidine cpds. and medicinal use thereof*. WO 0242297.

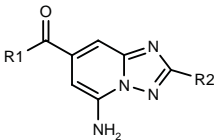
323055

1-[5-Amino-2-(5-bromofuran-2-yl)[1,2,4]triazolo[1,5-a]pyridin-7-yl]-1-[2(R)-(methoxymethyl)pyrrolidin-1-yl]-methanone



C17 H18 Br N5 O3; Mol wt: 420.2652

ACTION – Selective adenosine A_{2A} receptor antagonist (K_i = 2.4 nM at human A_{2A} receptors expressed in CHO cells), exhibiting 120-fold selectivity over A₁ receptors. Potentially useful for the treatment of CNS disorders including depression, neurodegenerative disorders and Parkinson’s disease. Other exemplified compounds are:



Compound	R1	R2	Formula
323056	2-Cl-PhCH ₂ CH ₂ NH	2-Pyr	C ₂₀ H ₁₇ ClN ₆ O
323057	cyclohexyl-N(Me)	5-Me-2-furyl	C ₁₉ H ₂₃ N ₅ O ₂
323058	1-pyrrolidinyl	Ph	C ₁₇ H ₁₇ N ₅ O
323059	2-Br-PhCH ₂ NH	5-Me-2-thienyl	C ₁₉ H ₁₆ BrN ₅ OS
323060	N(Me)Et	5-Cl-2-furyl	C ₁₄ H ₁₄ ClN ₆ O ₂
323061	4-(NH ₂ CO)-1-Pip	5-Br-2-furyl	C ₁₇ H ₁₇ BrN ₆ O ₃
323062	perhydo-2-isoquinolinyl	5-Br-2-furyl	C ₂₀ H ₂₂ BrN ₅ O ₂
323063	2(S)-(MeOCH ₂)-1-pyrrolidinyl	2-thiazolyl	C ₁₆ H ₁₈ N ₆ O ₂ S

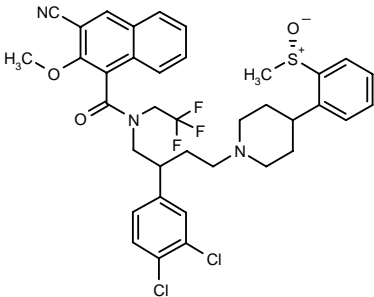
SOURCE – Roche.

REFERENCES

1. Brodbeck, B. and Nettekoven, M.H. (F. Hoffmann-La Roche AG) *Amino-triazolopyridine derivs. as adenosine receptor ligands*. WO 0248145.

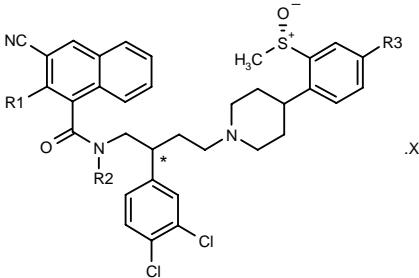
323652

(S₈)-3-Cyano-N-[2-(3,4-Dichlorophenyl)-4-[4-[2-(methylsulfinyl)phenyl]piperidin-1-yl]butyl]-2-methoxy-N-(2,2,2-trifluoroethyl)naphthalene-1-carboxamide

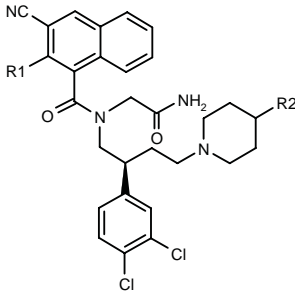


C37 H36 Cl2 F3 N3 O3 S; Mol wt: 730.6754

ACTION – Tachykinin NK₁ receptor antagonist, potentially useful for the treatment of depression, anxiety, stress disorders, eating disorders, bipolar disorder, drug abuse, schizophrenia, movement disorders, cognitive disorders, obesity, emesis, rheumatoid arthritis, cancer, edema, allergic rhinitis, inflammation, pain, gastrointestinal hypermotility, Huntington’s disease, chronic obstructive pulmonary disease, hypertension, migraine, bladder hypermotility and urticaria. Other exemplified compounds are:



Compound	R1	R2	R3	*Isomer	X	Formula
323653	OMe	CH ₂ CO ₂ Me	H			C ₃₈ H ₃₉ Cl ₂ N ₃ O ₅ S
323654	H	CH ₂ CO ₂ Me	OMe	S		C ₃₈ H ₃₉ Cl ₂ N ₃ O ₅ S
323658	Et	2-OH-Ph	OMe	S		C ₄₃ H ₄₃ Cl ₂ N ₃ O ₄ S
323660	OMe	CH ₂ CON(Me) ₂	OMe	S	citrate	C ₄₀ H ₄₄ Cl ₂ N ₄ O ₅ S.C ₆ H ₈ O ₇



Compound	R1	R2	Formula
323655	OMe	3-F-2-(MeSO)-Ph	C ₃₇ H ₃₇ Cl ₂ FN ₄ O ₄ S
323656	H	2-oxohexahydro-1-pyrimidinyl	C ₃₃ H ₃₆ Cl ₂ N ₆ O ₃
323657	H	2-OH-Ph	C ₃₅ H ₃₄ Cl ₂ N ₄ O ₃
323659	Et	2-F-4-(MeSO)-5-(NH ₂ CO)-Ph	C ₃₉ H ₄₀ Cl ₂ FN ₅ O ₄ S

SOURCE – AstraZeneca.

REFERENCES

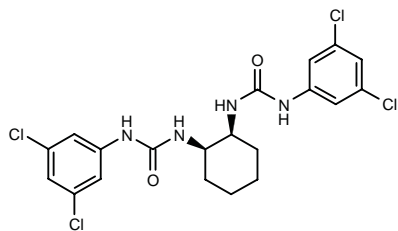
1. Shenvi, A.B. (AstraZeneca AB) *Compounds*. WO 0251807.

NEUROLOGIC DRUGS

TREATMENT OF EXTRAPYRAMIDAL MOVEMENT DISORDERS

322451

cis-1,1'-(Cyclohexane-1,2-diyl)bis[3-(3,5-dichlorophenyl)-urea]



C20 H20 Cl4 N4 O2; Mol wt: 490.2160

ACTION – A representative compound from a series of agents with affinity for cyclophilin-type immunophilin proteins (CyP). Compound inhibited CyP and CyPA rotamase activities with respective IC₅₀ values of about 560 and 4180 nM. It completely protected rat spinal cord slices from THA-induced cell death at 10 μM. In an MPTP-lesioned mouse model of Parkinson’s disease, compound provided 72.4% protection at 10 mg/kg s.c. By virtue of its neurotrophic activity, it may have potential in the treatment of neurodegenerative disorders such as Parkinson’s disease, Alzheimer’s disease and amyotrophic lateral sclerosis, demyelinating diseases including multiple sclerosis, and also ischemic stroke, spinal cord injury, edema, diabetic neuropathy, neuropathy associated with viral infection or drug therapy, and other disorders associated with degeneration of nervous system cells.

SOURCE – Guilford.

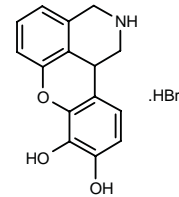
REFERENCES

1. Hamilton, G.S. et al. (Guilford Pharmaceuticals Inc.) *Bisubstd. carbocyclic cyclophilin binding cpds. and their use*. WO 0244126.

DINOXYLINE

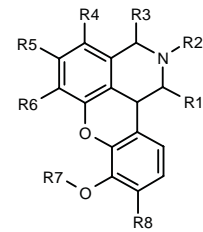
324237

1,2,3,11b-Tetrahydro-1-benzopyrano[4,3,2-*de*]isoquinoline-8,9-diol hydrobromide



C15 H13 N O3 . HBr; Mol wt: 336.1836

ACTION – Dopamine D1 receptor full agonist that demonstrated functional selectivity for this receptor and was found to have significant antiparkinson effects in animal studies. Other exemplified chromeno[4,3,2-*de*]-isoquinolines are:



Compound	R1	R2	R3	R4	R5	R6	R7	R8	Formula
324239	Me	H	Pr	Me	Me	H	H	OH	C ₂₁ H ₂₅ NO ₃
324240	H	H	H	H	F	H	H	OH	C ₁₅ H ₁₂ FNO ₃
324241	H	Me	H	Me	Br	H	H	OMe	C ₁₈ H ₁₈ BrNO ₃
324242	Pr	H	Pr	H	OH	H	H	OH	C ₂₁ H ₂₅ NO ₄
324243	H	H	H	H	H	H	H	H	C ₁₅ H ₁₃ NO ₂
324244	H	H	H	H	H	H	i-Pr	OH	C ₁₈ H ₁₉ NO ₃
324245	H	cyclopropyl	H	H	Et	H	H	OH	C ₂₀ H ₂₁ NO ₃
324246	H	cyclopropyl	H	OMe	H	Et	H	OH	C ₂₁ H ₂₃ NO ₄

SOURCES – University of North Carolina, Chapel Hill, NC (US); Purdue Research Foundation, West Lafayette, IN (US).

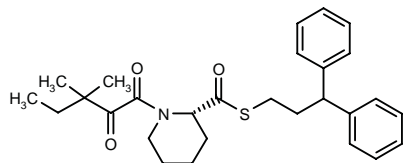
REFERENCES

1. Nichols, D.E. et al. (Purdue Research Foundation;University of North Carolina) *Chromeno[4,3,2-de]isoquinolines as potent dopamine receptor ligands*. US 6413977.

GPI-1511

323530

1-(3,3-Dimethyl-2-oxopentanoyl)piperidine-2(*S*)-carbothioic acid *S*-(3,3-diphenylpropyl) ester



C28 H35 N O3 S; Mol wt: 465.6545

SOURCE – AstraZeneca.

REFERENCES

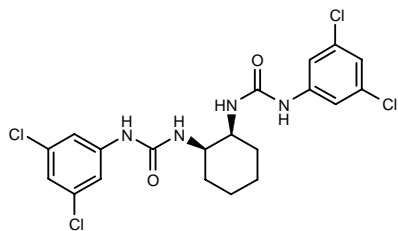
1. Shenvi, A.B. (AstraZeneca AB) *Compounds*. WO 0251807.

NEUROLOGIC DRUGS

TREATMENT OF EXTRAPYRAMIDAL MOVEMENT DISORDERS

322451

cis-1,1'-(Cyclohexane-1,2-diyl)bis[3-(3,5-dichlorophenyl)-urea]



C20 H20 Cl4 N4 O2; Mol wt: 490.2160

ACTION – A representative compound from a series of agents with affinity for cyclophilin-type immunophilin proteins (CyP). Compound inhibited CyP and CyPA rotamase activities with respective IC₅₀ values of about 560 and 4180 nM. It completely protected rat spinal cord slices from THA-induced cell death at 10 μM. In an MPTP-lesioned mouse model of Parkinson’s disease, compound provided 72.4% protection at 10 mg/kg s.c. By virtue of its neurotrophic activity, it may have potential in the treatment of neurodegenerative disorders such as Parkinson’s disease, Alzheimer’s disease and amyotrophic lateral sclerosis, demyelinating diseases including multiple sclerosis, and also ischemic stroke, spinal cord injury, edema, diabetic neuropathy, neuropathy associated with viral infection or drug therapy, and other disorders associated with degeneration of nervous system cells.

SOURCE – Guilford.

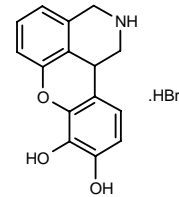
REFERENCES

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DINOXYLINE

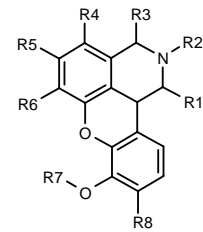
324237

1,2,3,11b-Tetrahydro-1-benzopyrano[4,3,2-*de*]isoquinoline-8,9-diol hydrobromide



C15 H13 N O3 . HBr; Mol wt: 336.1836

ACTION – Dopamine D1 receptor full agonist that demonstrated functional selectivity for this receptor and was found to have significant antiparkinson effects in animal studies. Other exemplified chromeno[4,3,2-*de*]-isoquinolines are:



Compound	R1	R2	R3	R4	R5	R6	R7	R8	Formula
324239	Me	H	Pr	Me	Me	H	H	OH	C ₂₁ H ₂₅ NO ₃
324240	H	H	H	H	F	H	H	OH	C ₁₅ H ₁₂ FNO ₃
324241	H	Me	H	Me	Br	H	H	OMe	C ₁₈ H ₁₈ BrNO ₃
324242	Pr	H	Pr	H	OH	H	H	OH	C ₂₁ H ₂₅ NO ₄
324243	H	H	H	H	H	H	H	H	C ₁₅ H ₁₃ NO ₂
324244	H	H	H	H	H	H	i-Pr	OH	C ₁₈ H ₁₉ NO ₃
324245	H	cyclopropyl	H	H	Et	H	H	OH	C ₂₀ H ₂₁ NO ₃
324246	H	cyclopropyl	H	OMe	H	Et	H	OH	C ₂₁ H ₂₃ NO ₄

SOURCES – University of North Carolina, Chapel Hill, NC (US); Purdue Research Foundation, West Lafayette, IN (US).

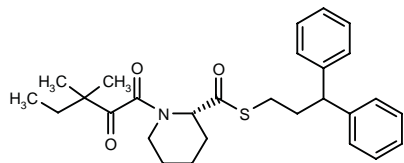
REFERENCES

1. Nichols, D.E. et al. (Purdue Research Foundation;University of North Carolina) *Chromeno[4,3,2-de]isoquinolines as potent dopamine receptor ligands*. US 6413977.

GPI-1511

323530

1-(3,3-Dimethyl-2-oxopentanoyl)piperidine-2(*S*)-carbothioic acid *S*-(3,3-diphenylpropyl) ester



C28 H35 N O3 S; Mol wt: 465.6545

ACTION – Neuroregenerative agent, an FKBP12 rotamase (FK-506-binding protein) inhibitor ($K_i = 86$ nM) able to produce 72-81% recovery of striatal dopaminergic innervation in the murine MPTP model of Parkinson's disease at a dose of 10 mg/kg p.o. Compound exhibited good oral bioavailability and readily crossed the blood-brain barrier. Potentially useful for the treatment of neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease, stroke, multiple sclerosis and peripheral neuropathies.

SOURCE – Guilford.

REFERENCES

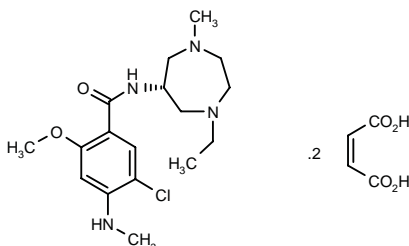
1. Ross, D.T. et al. (GPI Nil Holdings, Inc.) *Heterocyclic thioesters or ketones for vision and memory disorders*. JP 2002522525, US 6384056, WO 0009479.

2. Hamilton, G.S. et al. *Synthesis of N-glyoxyl prolyl and pipecolyl amides and thioesters and evaluation of their in vitro and in vivo nerve regenerative effects*. J Med Chem 2002, 45(16): 3549.

TREATMENT OF NAUSEA AND VOMITING

233481

5-Chloro-*N*-(1-ethyl-4-methylperhydro-1,4-diazepin-6(*R*)-yl)-2-methoxy-4-(methylamino)benzamide dimaleate



C₁₇ H₂₇ Cl N₄ O₂ · 2 C₄ H₄ O₄; Mol wt: 587.0225

ACTION – Antiemetic agent, a dual antagonist at dopamine D₂ and 5-HT₃ receptors ($IC_{50} = 34.6$ and 2.86 nM, respectively) with high selectivity over 5-HT₄ receptors ($IC_{50} > 1$ μM). In dogs, compound completely inhibited apomorphine-induced emesis at a dose of 1 mg/kg p.o. ($ED_{50} = 0.13$ mg/kg).

SOURCE – Dainippon Pharmaceutical.

REFERENCES

1. Yoshida, N. et al. (Dainippon Pharmaceutical Co., Ltd.) *Morphine-like drug-induced vomiting inhibitors containing (R)-1-ethyl-4-methylhexahydro-1H-1,4-diazepine derivs. as active ingredient*. JP 1998203987.

2. Hirokawa, Y. et al. *A novel series of N-(hexahydro-1,4-diazepin-6-yl) and N-(hexahydroazepin-3-yl)benzamides with high affinity for 5-HT₃ and dopamine D₂ receptors*. Bioorg Med Chem Lett 1998, 8(6): 619.

3. Hirokawa, Y. et al. *Synthesis and structure-activity relationships of 4-amino-5-chloro-N-(1,4-dialkylhexahydro-1,4-diazepin-6-yl)-2-methoxybenzamide derivatives, novel and potent serotonin 5-HT₃ and dopamine D₂ receptors dual antagonist*. Chem Pharm Bull 2002, 50(7): 941.

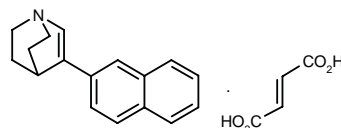
4. Hirokawa, Y. et al. *Synthesis and structure-activity relationships of N-(1-ethyl-4-methylhexahydro-1H-1, 4-diazepin-6-yl)amides with potent dopamine D₂ and serotonin 5-HT₃ receptor antagonistic activities*. AFMC Int Med Chem Symp (Sept 3-8, Tokyo) 1995, Abst P1M027.

TREATMENT OF COGNITION DISORDERS

322282

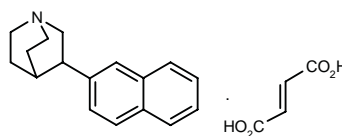
3-(2-Naphthyl)-1-azabicyclo[2.2.2]oct-2-ene fumarate

2,3-Didehydro-3-(2-naphthyl)quinuclidine fumarate



C₁₇ H₁₇ N · C₄ H₄ O₄; Mol wt: 351.3999

ACTION – Modulator of nicotinic acetylcholine receptors (particularly α₇ receptors) and/or monoamine transporters (DAT, SERT and NET). Compound was shown to inhibit the binding of [³H]-epibatidine (nonselective), [³H]-cytisine (α₄β₂-selective) and [³H]-α-bungarotoxin (α₇-selective) to nicotinic receptors with respective IC_{50} values of 17, 10 and 0.058 μM, proving its selectivity for the α₇ subtype. Potentially useful for the treatment of a variety of CNS disorders, conditions associated with smooth muscle contraction, endocrine disorders, neurodegenerative disorders, inflammation, pain and withdrawal symptoms related to tobacco, opioids, benzodiazepines and alcohol abuse. Another exemplified 3-substituted quinuclidine derivative is:



322285: C₁₇ H₁₉ N · C₄ H₄ O₄

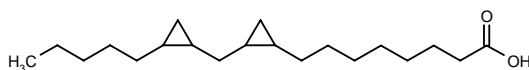
SOURCE – NeuroSearch.

REFERENCES

1. Peters, D. et al. (NeuroSearch A/S) *3-Substd. quinuclidines and their use as nicotinic agonists*. WO 0244176.

323256

8-[2-(2-Pentylcyclopropylmethyl)cyclopropyl]octanoic acid



C₂₀ H₃₆ O₂; Mol wt: 308.5024

ACTION – A representative comopund from a series of cyclopropyl-containing carboxylic acid derivatives able to stimulate long-term potentiation (LTP) of synaptic transmission. The compound increased the population spike amplitude by 200% following i.p. administration to anesthetized mice at a dose of 1 mg/kg, suggesting induction of LTP-like potentiation of hippocampal neurotransmission. Potentially useful for the treatment of dementia including senile dementia, Alzheimer’s disease, cerebrovascular dementia, posttraumatic dementia, dementia associated with brain tumor, chronic subdural hematoma and normal-pressure hydrocephalus, post-cephalomeningitis dementia and Parkinson’s disease, and also learning and memory disorders.

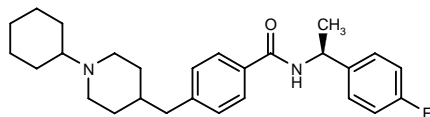
SOURCE – Fujisawa.

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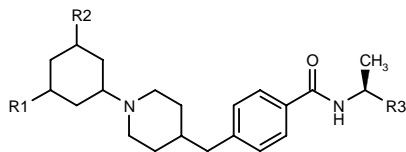
323674

4-(1-Cyclohexylpiperidin-4-ylmethyl)-N-[1 (S)-(4-fluorophenyl)ethyl]benzamide

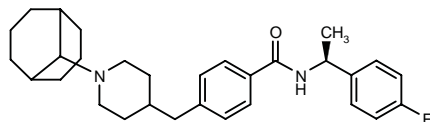


C27 H35 F N2 O; Mol wt: 422.5845

ACTION – Muscarinic receptor antagonist with potential in the treatment of cognitive and neurodegenerative disorders. Other specifically claimed compounds are:



Compound	R1	R2	R3	Formula
323675	(R)-Me	(S)-Me	4-F-Ph	C ₂₉ H ₃₉ FN ₂ O
323676	(R)-CF3	(S)-CF3	4-F-Ph	C ₂₉ H ₃₃ F ₇ N ₂ O
323677	H	Me	cyclohexyl	C ₂₈ H ₄₄ N ₂ O
323680	H	H	cyclohexyl	C ₂₇ H ₄₂ N ₂ O
323681	H	(S)-Me	cyclohexyl	C ₂₈ H ₄₄ N ₂ O



323679: C30 H39 F N2 O

SOURCE – Schering-Plough.

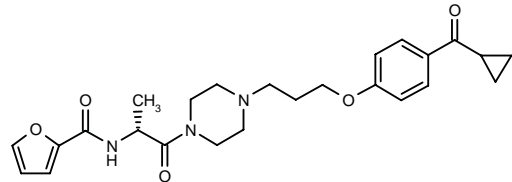
REFERENCES

1. McKittrick, B.A. et al. (Schering Corp.) *Muscarinic antagonists*. WO 0251808.

A-317920*

310132

N-[2-[4-[3-[4-(Cyclopropylcarbonyl)phenoxy]propyl]piperazin-1-yl]-1(R)-methyl-2-oxoethyl]furan-2-carboxamide



C25 H31 N3 O5; Mol wt: 453.5359

ACTION – Potent and selective histamine H₃ receptor antagonist with subnanomolar affinity for rat cortex H₃ receptors (K_i = 0.71) and high selectivity over human cloned H₁ and H₂ receptors (K_i > 1000 nM), as well as a panel of other receptors and transporters. In functional studies, compound antagonized K⁺-evoked depolarization-induced [³H]-histamine release from rat synaptosomes with a pK_b value of 9.20. A favorable pharmacokinetic profile with good bioavailability (31.9%) was seen in rats dosed orally with 10 mg/kg. Preliminary behavioral experiments in rats demonstrated that compound at 3 and 10 mg/kg s.c. dose-dependently improved cognitive performance in a passive avoidance test. No phospholipidosis was seen in rat hepatocytes treated for 24 h with 25 μM. Potentially useful for the treatment of Alzheimer’s disease or attention deficit hyperactivity disorder.

SOURCE – Abbott.

REFERENCES

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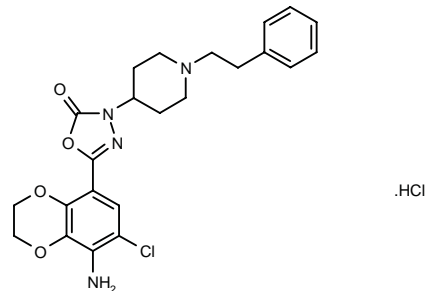
2. Black, L.A. et al. *Acyl-D-alanine amides: Selective histamine H3 receptor antagonists*. 224th ACS Natl Meet (Aug 18-22, Boston) 2002, Abst MEDI 323.

*Identified compound **310132** (see **310131**) Drug Data Rep 2001, 023(11): 1066.

SL-65.0155

287996

5-(8-Amino-7-chloro-2,3-dihydro-1,4-benzodioxin-5-yl)-3-[1-(2-phenylethyl)piperidin-4-yl]-1,3,4-oxadiazol-2(3H)-one hydrochloride



C23 H25 Cl N4 O4 . HCl; Mol wt: 493.3884

ACTION – 5-HT₄ receptor partial agonist with high affinity for human 5-HT₄ receptors ($K_i = 0.6$ nM) and good selectivity (> 100-fold) over other 5-HT receptor subtypes. Partial agonist activity was seen in CHO cells expressing human 5-HT₄ receptors, where compound stimulated cAMP production with a maximal effect of 40-50% that of 5-HT; 5-HT₄ receptor antagonism was seen in peripheral tissues including rat esophagus ($pK_b = 8.81$) and guinea pig ileum ($pK_b = 8.29$). *In vivo*, compound improved performance in several rodent models of learning and memory including the object recognition task in rats, where compound (0.001-0.1 mg/kg i.p or p.o.) improved retention at 24 h, the linear maze task in aged rats, where it improved task performance at 0.01 and 0.1 mg/kg i.p., and the water maze task in mice, where it significantly reversed scopolamine-induced deficits at 0.1 and 0.3 mg/kg i.p. At pharmacologically active doses, compound did not exhibit cardiovascular side effects in conscious normotensive rats or anesthetized dogs, and no significant effects on gastrointestinal motility were observed in rats. Potentially useful for the treatment of Alzheimer's disease.

SOURCE – Sanofi-Synthélabo.

REFERENCES

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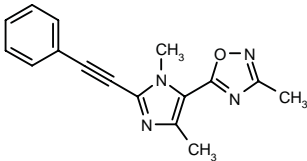
2. Moser, P.C. et al. *SL65.0155, a novel 5-hydroxytryptamine₄ receptor partial agonist with potent cognition-enhancing properties*. J Pharmacol Exp Ther 2002, 302(2): 731.

3. *Sanofi-Synthelabo presents overhauled R&D portfolio to financial analysis*. DailyDrugNews.com (Daily Essentials) 2000, March 21.

TREATMENT OF
CEREBROVASCULAR DISEASES

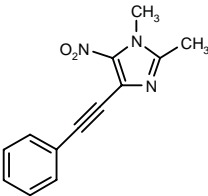
322774

5-[1,4-Dimethyl-2-(2-phenylethynyl)-1*H*-imidazol-5-yl]-3-methyl-1,2,4-oxadiazole



C16 H14 N4 O; Mol wt: 278.3136

ACTION – Metabotropic glutamate mGluR₅ (mglu₅) receptor antagonist ($IC_{50} = 0.011$ μ M), potentially useful for the treatment of Alzheimer's disease, senile dementia, acute and chronic pain, Parkinson's disease, Huntington's chorea, cerebral ischemia, amyotrophic lateral sclerosis, multiple sclerosis, head and spinal cord injury, hypoxia caused by pregnancy, cardiac arrest, hypoglycemia and also psychiatric disorders such as psychosis, epilepsy, schizophrenia, anxiety and depression. Another exemplified compound is:



322779: C13 H11 N3 O2

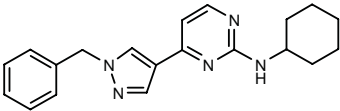
SOURCE – Roche.

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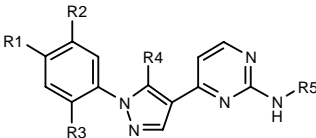
322890

4-(1-Benzyl-1*H*-pyrazol-4-yl)-*N*-cyclohexylpyrimidin-2-amine



C20 H23 N5; Mol wt: 333.4367

ACTION – An inhibitor of c-Jun *N*-terminal kinase (JNK) with selectivity over p38 kinase. Potentially useful for the treatment of a broad range of disorders including neurodegenerative diseases, inflammatory, autoimmune, proliferative and infectious diseases, destructive bone disorders, allergies, stroke, heart attacks, angiogenesis, organ hypoxia, vascular hyperplasia, cardiac hypertrophy and thrombin-induced platelet aggregation. Other exemplified compounds are:



Compound	R1	R2	R3	R4	R5	Formula
322891	H	H	H	H	cyclohexyl	C ₁₉ H ₂₁ N ₅
322892	OMe	H	H	H	cyclohexyl	C ₂₀ H ₂₃ N ₅ O
322893	H	Cl	Cl	H	cyclohexyl	C ₁₉ H ₁₉ Cl ₂ N ₅
322895	F	H	F	H	cyclohexyl	C ₁₉ H ₁₉ F ₂ N ₅
322896	H	H	H	Me	4-F-Ph	C ₂₀ H ₁₆ FN ₅
322897	H	H	H	Me	4-Cl-Ph	C ₂₀ H ₁₆ ClN ₅
322898	H	H	H	Me	4-NO ₂ -Ph	C ₂₀ H ₁₆ N ₅ O ₂

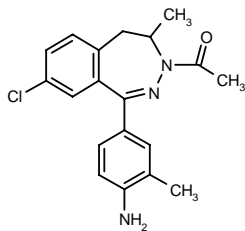
SOURCE – Vertex.

REFERENCES

1. Ledeboer, M. et al. (Vertex Pharmaceuticals Inc.) *Inhibitors of C-Jun N-terminal kinases (JNK) and other protein kinases*. WO 0246184.

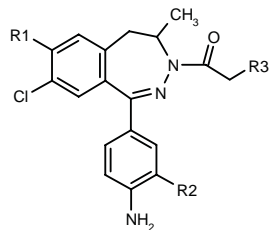
323318

1-[1-(4-Amino-3-methylphenyl)-8-chloro-4-methyl-4,5-dihydro-3*H*-2,3-benzodiazepin-3-yl]ethanone



C19 H20 Cl N3 O; Mol wt: 341.8400

ACTION – AMPA receptor antagonist with *in vivo* activity in a mouse model of MgCl₂-induced global cerebral ischemia, giving a PD₅₀ value (dose that prolonged survival by 50%) of 4.6 mg/kg i.p. This compound was shown to have a duration of action of 20 h, as determined by measuring the decrease in body temperature following i.p. administration to rats. Potentially useful for the treatment of anxiety, Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis, stroke, acute head injury, epilepsy, schizophrenia, emesis, migraine and urinary disorders. Other exemplified benzodiazepine derivatives are:



Compound	R1	R2	R3	Formula
323319	H	Me	Me	C ₂₀ H ₂₂ ClN ₃ O
323320	H	H	Me	C ₁₉ H ₂₀ ClN ₃ O
323321	Cl	Me	H	C ₁₉ H ₁₉ Cl ₂ N ₃ O
323322	Cl	H	H	C ₁₈ H ₁₇ Cl ₂ N ₃ O

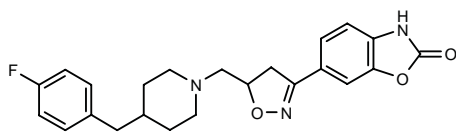
SOURCE – Egis.

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323378

(+)-6-[5-[4-(4-Fluorobenzyl)piperidin-1-ylmethyl]-4,5-dihydroisoxazol-3-yl]benzoxazol-2(3*H*)-one



C23 H24 F N3 O3; Mol wt: 409.4586

ACTION – Selective NMDA antagonist shown to inhibit [³H]-ifenprodil binding to NMDA receptors in rat brain preparations with an IC₅₀ of 0.016 μM. Compound also demonstrated *in vivo* activity in the rat formalin test of analgesia (10 mg/kg p.o.) and in the 6-OHDA-lesioned rat model of Parkinson's disease (MED < 30 mg/kg p.o.). Potentially useful for the treatment of stroke, cerebral ischemia, depression, CNS trauma, hypoglycemia, neurodegenerative disorders such as Parkinson's disease, anxiety, migraine, convulsions, psychosis, glaucoma, pain, urinary incontinence, aminoglycoside antibiotic-induced hearing loss, CMV retinitis, and opioid tolerance or withdrawal.

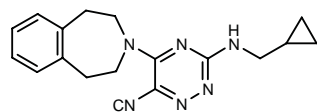
SOURCE – Pfizer.

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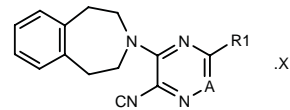
323801

3-(Cyclopropylmethylamino)-5-(2,3,4,5-tetrahydro-1*H*-3-benzazepin-3-yl)-1,2,4-triazine-6-carbonitrile



C18 H20 N6; Mol wt: 320.3980

ACTION – Metabotropic glutamate receptor mGluR₁ (mglu₁) antagonist (IC₅₀ = 0.005 μM), potentially useful for the treatment of neurological disorders such as epilepsy, stroke, acute and chronic pain, psychosis, Alzheimer's disease and cognition disorders. Other exemplified compounds are:



Compound	R1	A	X	Formula
323802	OCH2CH2OMe	N		C ₁₇ H ₁₉ N ₅ O ₂
323803	NH2	N		C ₁₄ H ₁₄ N ₆
323804	N(Me)2	N		C ₁₆ H ₁₈ N ₆
323805	NHCH2CH2OH	N		C ₁₆ H ₁₈ N ₆ O
323806	NHCH2CH(OH)Me	N		C ₁₇ H ₂₀ N ₆ O
323807	NHNH2	N		C ₁₄ H ₁₅ N ₇
323808	t-BuOCONHCH2CH2NH	N		C ₂₁ H ₂₇ N ₇ O ₂
323809	3-Pyr-CH2CH2NH	N		C ₂₁ H ₂₁ N ₇
323810	OH	N		C ₁₄ H ₁₃ N ₅ O
323811	NHCH2CH2NH2	N	CF3CO2H	C ₁₆ H ₁₉ N ₇ C ₂ HF ₃ O ₂
323812	Et	C(Me)		C ₁₈ H ₂₀ N ₄
323813	Me	C(Et)		C ₁₈ H ₂₀ N ₄
323814	H	CH		C ₁₅ H ₁₄ N ₄
323815	Me	C(Ph)		C ₂₂ H ₂₀ N ₄
323816	NHCH2CH2OH	CH		C ₁₇ H ₁₉ N ₅ O

SOURCE – Roche.

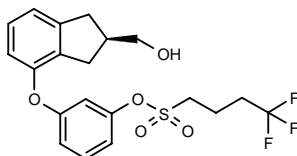
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BAY-38-7271

322598

(-)-4,4,4-Trifluorobutane-1-sulfonic acid 3-[2(*R*)-(hydroxymethyl)-2,3-dihydro-1*H*-inden-4-yloxy]phenyl ester



C20 H21 F3 O5 S; Mol wt: 430.4409

ACTION – Cannabinoid receptor agonist with high affinity for native rat and human CB₁ receptors (K_i = 0.46 and 1.09 nM, respectively), as well as for recombinant human CB₁ and CB₂ receptors (K_i = 1.85 and 5.96 nM, respectively). Compound exhibited full agonist activity at rat and human CB₁ receptors, with respective EC₅₀ values of 7.55 and 15.8 nM. *In vivo*, it dose-dependently reduced body temperature with a minimal effective dose (MED) of 6 µg/kg i.v., and in rats trained to discriminate the CB₁/CB₂ receptor agonist CP-55940, compound induced complete discrimination at 3 µg/kg i.v.; these effects were inhibited by pretreatment with a selective CB₁ receptor antagonist. In addition, compound reduced infarct volume in a rat traumatic brain injury model, producing a 70% decrease at 100 ng/kg/h by 4-h infusion starting immediately after induction of subdural hematoma; significant neuroprotective efficacy was also seen when administration was delayed for 3 h (59% reduction in infarct volume at 300 ng/kg/h). It also significantly reduced infarct volume (27% at 1000 ng/kg/h) in a rat model of focal cerebral ischemia. Potentially useful as a neuroprotective agent devoid of cannabinoid-like side effects.

SOURCE – Bayer.

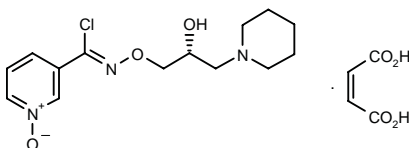
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BRX-220

320339

N-[2(*R*)-Hydroxy-3-(1-piperidinyl)propoxy]-3-pyridine-carboximidoyl chloride 1-oxide maleate (1:1)



C14 H20 Cl N3 O3 . C4 H4 O4; Mol wt: 429.8546

ACTION – Nontoxic heat shock protein (HSP) coinducer, an analogue of bimoclomol with protective activity in experimental models of ischemic disease, diabetic complications and pancreatitis. In a model of injury-induced neurodegeneration of motoneurons in rat pups, compound (2-10 mg/kg i.p.) protected neurons from axotomy-induced cell death and significantly increased the expression of HSP70 and HSP90 in glia and neurons. In a model of cholecystokinin-induced pancreatitis in rats, compound (20 mg/kg p.o.) significantly attenuated the morphological changes induced by CCK, increased pancreatic levels of HSP60 and HSP72, total protein content, amylase and trypsinogen activities, plasma levels of trypsinogen activation peptide, and reduced lipid peroxidation, protein oxidation and Cu/Zn superoxide dismutase activity. It was also active in a model of peripheral neuropathy and insulin resistance in diabetic rats.

SOURCE – Biorex R&D.

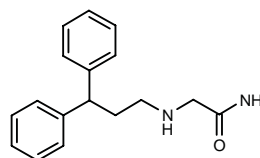
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N20C

322597

*N*²-(3,3-Diphenylpropyl)glycinamide



C17 H20 N2 O; Mol wt: 268.3580

ACTION – Neuroprotective agent, an NMDA receptor blocker (IC_{50} = 5 mM) with selectivity over GluR1-mediated ion currents, capsaicin-activated VR1 responses, voltage-dependent Ca^{2+} , Na^{+} or K^{+} channels. Compound did not act as a competitive glutamate or glycine antagonist, but as a competitive open channel blocker, binding at the same site as dizolcipine (MK-801). In cultured rat cerebellar neurons, it prevented L-glutamate-induced neuronal death by blocking NMDA receptor channel activity and preventing neuronal Ca^{2+} overload and subsequent nitric oxide and cGMP formation. *In vivo*, compound exhibited neuroprotective activity in a mouse model of ammonia-induced hepatic encephalopathy, dose-dependently (5-50 mg/kg i.p.) preventing excitotoxicity. Potentially useful for the treatment of neurodegenerative disorders.

SOURCES – CSIC, Madrid (ES); Universidad de Extremadura, Badajoz (ES); Fundación Valenciana de Investigaciones Biomédicas, Valencia (ES); Universidad Miguel Hernández, Elche (ES); Universidad de Valencia, Valencia (ES).

REFERENCES

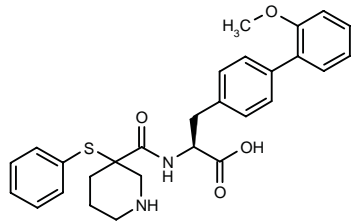
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RESPIRATORY DRUGS

TREATMENT OF UPPER
RESPIRATORY TRACT DISORDERS

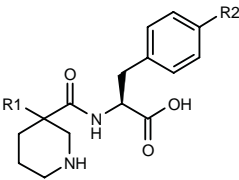
322611

4-(2-Methoxyphenyl)-N-[3-(phenylsulfanyl)piperidin-3-ylcarbonyl]-L-phenylalanine



C28 H30 N2 O4 S; Mol wt: 490.6210

ACTION – $\alpha_4\beta_1$ (VLA-4), $\alpha_4\beta_7$ (LPAM-1) and/or $\alpha_9\beta_1$ integrin antagonist, claimed for use in the treatment of cell adhesion-mediated disorders, particularly allergic rhinitis, multiple sclerosis, atherosclerosis, inflammation and inflammatory bowel disease. Other exemplified substituted nipecotyl derivatives are:



Compound	R1	R2	Formula
322612	3-Br-PhSO2	2,6-(MeO)2-Ph	C ₂₉ H ₃₁ BrN ₂ O ₇ S
322614	4-(1-pyrrolidinyl)-PhSO2	2,6-(MeO)2-Ph	C ₃₃ H ₃₉ N ₃ O ₇ S
322615	4-morpholinyl-CH2CH2SO2	2,6-(MeO)2-Ph	C ₂₉ H ₃₉ N ₃ O ₆ S
322616	1-imidazolyl-CH2CH2SO2	2,6-(MeO)2-Ph	C ₂₈ H ₃₄ N ₄ O ₇ S
322617	SO2CH2Ph	2,6-(MeO)2-Ph	C ₃₀ H ₃₄ N ₂ O ₇ S
322618	SPh	H	C ₂₁ H ₂₄ N ₂ O ₃ S
322619	SO2Ph	1-pyrrolidinyl-COO	C ₂₆ H ₃₁ N ₃ O ₇ S
322620	SO2Ph	2-Et-4-thiazolyl	C ₂₆ H ₂₉ N ₃ O ₅ S ₂

SOURCE – Merck & Co.

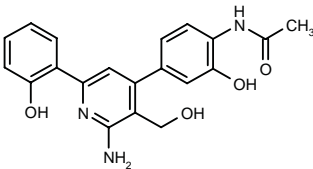
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ASTHMA THERAPY

322293

N-[4-[2-Amino-3-(hydroxymethyl)-6-(2-hydroxyphenyl)pyridin-4-yl]-2-hydroxyphenyl]acetamide



C20 H19 N3 O4; Mol wt: 365.3871

ACTION – Inhibitor of $I\kappa B$ kinase- β (IKK- β) and therefore able to prevent the activation of NF- κB . It inhibited the TNF- α -stimulated production of RANTES in human epithelial A549 cells with an IC_{50} < 1 μM , and the production of IL-2 in Jurkat T-cells stimulated with anti-CD3/anti-CD28 antibodies with an IC_{50} < 0.5 μM . Potentially useful for the treatment of inflammatory and immune disorders such as asthma, allergic rhinitis, atopic dermatitis, conjunctivitis, chronic rheumatism, systemic lupus erythematosus, psoriasis, systemic inflammatory response syndrome, sepsis, polymyositis, dermatomyositis, polyarthritis nodosa, mixed connective tissue disease, Sjögren's syndrome, gout, ischemia and cancer.

SOURCE – Bayer.

REFERENCES

1. Murata, T. et al. (Bayer AG) 4-Aryl pyridine derivs. JP 2002193938, WO 0244153.

ACTION – Neuroprotective agent, an NMDA receptor blocker (IC_{50} = 5 mM) with selectivity over GluR1-mediated ion currents, capsaicin-activated VR1 responses, voltage-dependent Ca^{2+} , Na^{+} or K^{+} channels. Compound did not act as a competitive glutamate or glycine antagonist, but as a competitive open channel blocker, binding at the same site as dizolcipine (MK-801). In cultured rat cerebellar neurons, it prevented L-glutamate-induced neuronal death by blocking NMDA receptor channel activity and preventing neuronal Ca^{2+} overload and subsequent nitric oxide and cGMP formation. *In vivo*, compound exhibited neuroprotective activity in a mouse model of ammonia-induced hepatic encephalopathy, dose-dependently (5-50 mg/kg i.p.) preventing excitotoxicity. Potentially useful for the treatment of neurodegenerative disorders.

SOURCES – CSIC, Madrid (ES); Universidad de Extremadura, Badajoz (ES); Fundación Valenciana de Investigaciones Biomédicas, Valencia (ES); Universidad Miguel Hernández, Elche (ES); Universidad de Valencia, Valencia (ES).

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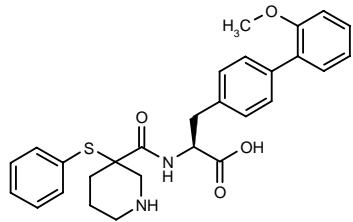
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RESPIRATORY DRUGS

TREATMENT OF UPPER
RESPIRATORY TRACT DISORDERS

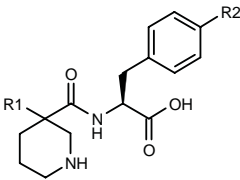
322611

4-(2-Methoxyphenyl)-N-[3-(phenylsulfanyl)piperidin-3-ylcarbonyl]-L-phenylalanine



C28 H30 N2 O4 S; Mol wt: 490.6210

ACTION – $\alpha_4\beta_1$ (VLA-4), $\alpha_4\beta_7$ (LPAM-1) and/or $\alpha_9\beta_1$ integrin antagonist, claimed for use in the treatment of cell adhesion-mediated disorders, particularly allergic rhinitis, multiple sclerosis, atherosclerosis, inflammation and inflammatory bowel disease. Other exemplified substituted nipecotyl derivatives are:



Compound	R1	R2	Formula
322612	3-Br-PhSO2	2,6-(MeO)2-Ph	C ₂₉ H ₃₁ BrN ₂ O ₇ S
322614	4-(1-pyrrolidinyl)-PhSO2	2,6-(MeO)2-Ph	C ₃₃ H ₃₉ N ₃ O ₇ S
322615	4-morpholinyl-CH2CH2SO2	2,6-(MeO)2-Ph	C ₂₉ H ₃₉ N ₃ O ₆ S
322616	1-imidazolyl-CH2CH2SO2	2,6-(MeO)2-Ph	C ₂₈ H ₃₄ N ₄ O ₇ S
322617	SO2CH2Ph	2,6-(MeO)2-Ph	C ₃₀ H ₃₄ N ₂ O ₇ S
322618	SPh	H	C ₂₁ H ₂₄ N ₂ O ₃ S
322619	SO2Ph	1-pyrrolidinyl-COO	C ₂₆ H ₃₁ N ₃ O ₇ S
322620	SO2Ph	2-Et-4-thiazolyl	C ₂₆ H ₂₉ N ₃ O ₅ S ₂

SOURCE – Merck & Co.

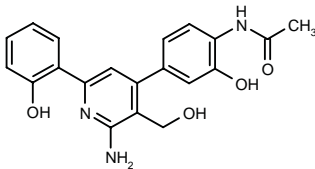
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ASTHMA THERAPY

322293

N-[4-[2-Amino-3-(hydroxymethyl)-6-(2-hydroxyphenyl)pyridin-4-yl]-2-hydroxyphenyl]acetamide



C20 H19 N3 O4; Mol wt: 365.3871

ACTION – Inhibitor of I κ B kinase- β (IKK- β) and therefore able to prevent the activation of NF- κ B. It inhibited the TNF- α -stimulated production of RANTES in human epithelial A549 cells with an IC_{50} < 1 μ M, and the production of IL-2 in Jurkat T-cells stimulated with anti-CD3/anti-CD28 antibodies with an IC_{50} < 0.5 μ M. Potentially useful for the treatment of inflammatory and immune disorders such as asthma, allergic rhinitis, atopic dermatitis, conjunctivitis, chronic rheumatism, systemic lupus erythematosus, psoriasis, systemic inflammatory response syndrome, sepsis, polymyositis, dermatomyositis, polyarthritis nodosa, mixed connective tissue disease, Sjögren's syndrome, gout, ischemia and cancer.

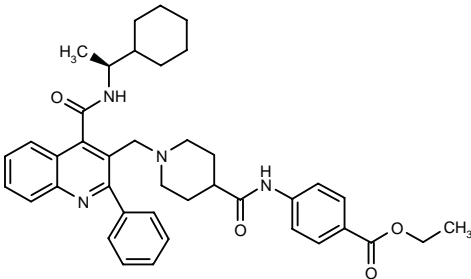
SOURCE – Bayer.

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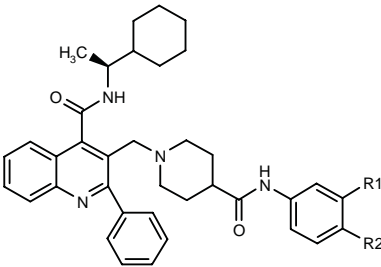
322508

4-[1-[4-[*N*-[1(*S*)-Cyclohexylethyl]carbamoyl]-2-phenylquinolin-3-ylmethyl]piperidin-4-ylcarboxamido]benzoic acid ethyl ester



C40 H46 N4 O4; Mol wt: 646.8274

ACTION – Tachykinin NK₂ and/or NK₃ receptor antagonist, potentially useful for the treatment of a broad range of disorders including, but not limited to, chronic obstructive pulmonary disease, asthma, cough, inflammation, psoriasis, arthritis, pain, allergy, ophthalmic diseases, skin disorders, transplant rejection, systemic lupus erythematosus, ulcerative colitis, Crohn’s disease, urinary incontinence, CNS disorders, multiple sclerosis, etc. Other exemplified compounds are:



Compound	R1	R2	Formula
322509	CO2Et	H	C ₄₀ H ₄₆ N ₄ O ₄
322510	H	CO2H	C ₃₈ H ₄₂ N ₄ O ₄
322511	CO2H	H	C ₃₈ H ₄₂ N ₄ O ₄

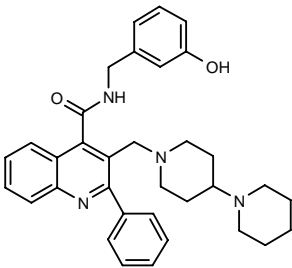
SOURCE – GlaxoSmithKline.

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1. Farina, C. et al. (GlaxoSmithKline SpA;Laboratoire GlaxoSmithKline SAS) *Novel cpds.* WO 0243734.

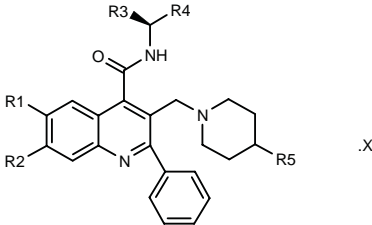
322513

3-(1,4'-Bipiperidin-1'-ylmethyl)-*N*-(3-hydroxybenzyl)-2-phenylquinoline-4-carboxamide



C34 H38 N4 O2; Mol wt: 534.7002

ACTION – Tachykinin NK₂ and/or NK₃ receptor antagonist, potentially useful for the treatment of a broad range of disorders including, but not limited to, chronic obstructive pulmonary disease, asthma, cough, inflammation, psoriasis, arthritis, pain, allergy, ophthalmic diseases, skin disorders, transplant rejection, systemic lupus erythematosus, ulcerative colitis, Crohn’s disease, urinary incontinence, CNS disorders, multiple sclerosis, etc. Other exemplified compounds are:



Compound	R1	R2	R3	R4	R5	X	Formula
322514	H	H	Me	(R)-CH(OH)Ph	1-Pip		C ₃₆ H ₄₂ N ₄ O ₂
322515	H	H	i-Pr	Ph	NH2		C ₃₂ H ₃₆ N ₄ O
322516	H	H	Me	Ph	2-oxo-1-pyrrolidinyl		C ₃₄ H ₃₆ N ₄ O ₂
322517	H	OCH2-CO2Et	Et	Ph	1-Pip		C ₄₀ H ₄₈ N ₄ O ₄
322518	H	OCH2-CONH2	Et	Ph	1-Pip	2HCl	C ₃₈ H ₄₅ N ₅ O ₃ ·2HCl
322519	H	Cl	Me	cyclohexyl	1-Pip		C ₃₅ H ₄₅ ClN ₄ O
322520	F	H	Me	cyclohexyl	1-Pip		C ₃₅ H ₄₅ FN ₄ O
322521	CF3	H	Me	cyclohexyl	1-Pip		C ₃₆ H ₄₅ F ₃ N ₄ O

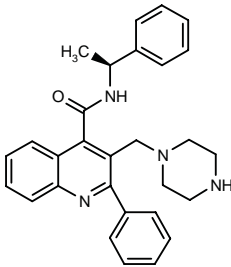
SOURCE – GlaxoSmithKline.

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1. Farina, C. et al. (GlaxoSmithKline SpA;Laboratoire GlaxoSmithKline SAS) *Novel cpds.* WO 0244154.

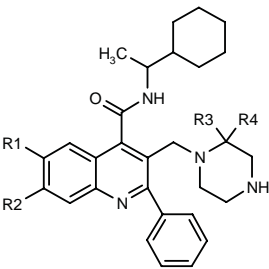
322522

2-Phenyl-*N*-[1(*S*)-phenylethyl]-3-(piperazin-1-ylmethyl)-quinoline-4-carboxamide

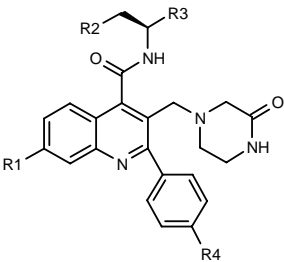


C29 H30 N4 O; Mol wt: 450.5830

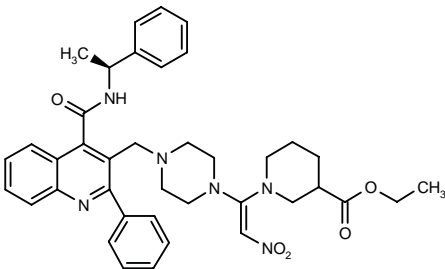
ACTION – Tachykinin NK₃ receptor antagonist, potentially useful for the treatment of a broad range of disorders including, but not limited to, chronic obstructive pulmonary disease, asthma, cough, inflammation, psoriasis, arthritis, pain, allergy, ophthalmic diseases, skin disorders, transplant rejection, systemic lupus erythematosus, ulcerative colitis, Crohn’s disease, urinary incontinence, CNS disorders, multiple sclerosis, etc. Other exemplified quinoline derivatives are:



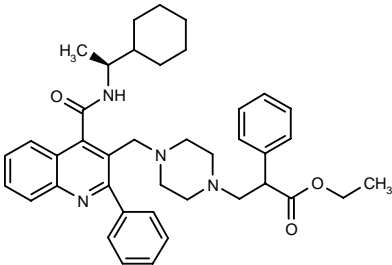
Compound	R1	R2	R3	R4	Isomer	Formula
322523	OMe	OMe	H	H	S	C ₃₁ H ₄₀ N ₄ O ₃
322526	Cl	H	H	H	S	C ₂₉ H ₃₅ ClN ₄ O
322527	H	H	-O-		S	C ₂₉ H ₃₄ N ₄ O ₂
322596	H	H	H	H	R	C ₂₉ H ₃₀ N ₄ O



Compound	R1	R2	R3	R4	Formula
322528	F	H	cyclohexyl	H	C ₂₉ H ₃₃ FN ₄ O ₂
322529	H	Me	Ph	H	C ₃₀ H ₃₀ N ₄ O ₂
322530	H	H	cyclohexyl	CF ₃	C ₃₀ H ₃₃ F ₃ N ₄ O ₂



322524: C39 H44 N6 O5



322525: C40 H48 N4 O3

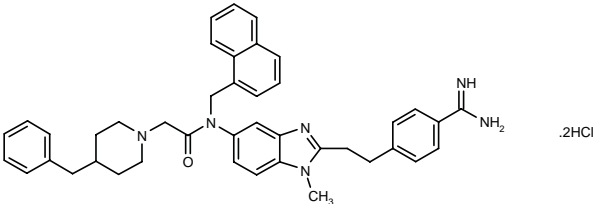
SOURCE – GlaxoSmithKline.

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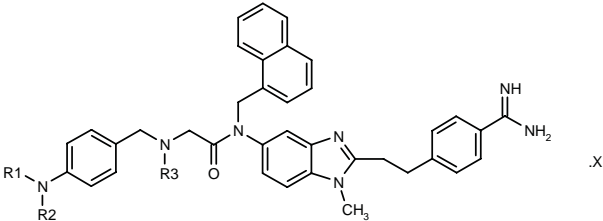
322961

N-[2-[2-(4-Amidinophenyl)ethyl]-1-methyl-1 H-benzimidazol-5-yl]-2-(4-benzylpiperidin-1-yl)-N-(naphthalen-1-ylmethyl)acetamide dihydrochloride



C42 H44 N6 O . 2HCl; Mol wt: 721.7724

ACTION – Tryptase inhibitor (IC₅₀ = 0.0039 μM), potentially useful for the treatment of inflammatory and allergic disorders including bronchial asthma, allergic rhinitis, allergic conjunctivitis, atopic dermatitis, urticaria, allergic otitis, allergic gastrointestinal disorders, Crohn's disease, ulcerative colitis, anaphylactic shock, septic shock, acute respiratory distress syndrome and arthritis. Other exemplified benzimidazoles are:



Compound	R1	R2	R3	X	Formula
322962	H	H	H	3HCl	C ₃₇ H ₃₇ N ₇ O.3HCl
322963	Et	Et	H	2HCl	C ₄₁ H ₄₅ N ₇ O.2HCl
322964	-(CH2)4-		H	2HCl	C ₄₁ H ₄₃ N ₇ O.2HCl
322965	-(CH2)4-		Me	2HCl	C ₄₂ H ₄₅ N ₇ O.2HCl

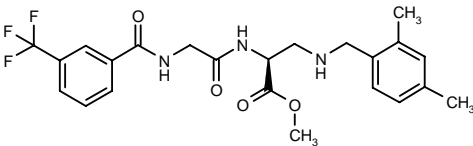
SOURCE – Boehringer Ingelheim.

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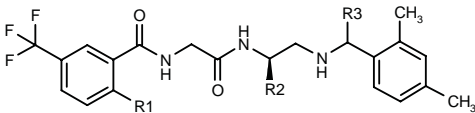
323360

N-[3-(Trifluoromethyl)benzoyl]glycyl-3-(2,4-dimethylbenzylamino)-L-alanine methyl ester



C23 H26 F3 N3 O4; Mol wt: 465.4694

ACTION – Chemokine CCR2 receptor antagonist, potentially useful for the treatment of inflammatory, allergic and autoimmune diseases, particularly asthma, multiple sclerosis, atherosclerosis and rheumatoid arthritis. Other exemplified diamines are:



Compound	R1	R2	R3	Formula
323361	H	t-BuNHCO	H	C ₂₆ H ₃₃ F ₃ N ₄ O ₃
323362	H	CO ₂ Me	Me	C ₂₄ H ₂₈ F ₃ N ₃ O ₄
323363	H	(R)-CH(OH)Me	H	C ₂₃ H ₂₈ F ₃ N ₃ O ₃
323364	H	(R)-CH(OH)Ph	H	C ₂₈ H ₃₀ F ₃ N ₃ O ₃
323365	t-BuOCONH	(R)-i-BuCH(OH)	H	C ₃₁ H ₄₃ F ₃ N ₄ O ₅

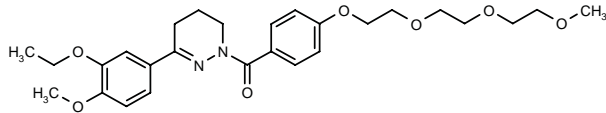
SOURCE – Bristol-Myers Squibb.

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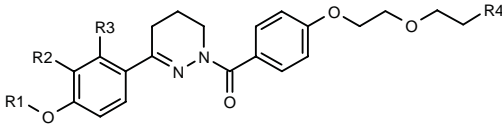
323703

1-[3-(3-Ethoxy-4-methoxyphenyl)-1,4,5,6-tetrahydropyridazin-1-yl]-1-[4-[2-[2-(2-methoxyethoxy)ethoxy]ethoxy]phenyl]methanone

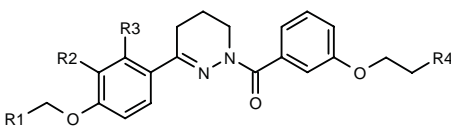


C27 H36 N2 O7; Mol wt: 500.5884

ACTION – Phosphodiesterase type 4 (PDE4) inhibitor considered to have potential in the treatment of disorders associated with reduced production of cAMP and/or TNF including allergic diseases, asthma, chronic bronchitis, atopic dermatitis, psoriasis, inflammation, rheumatoid arthritis, multiple sclerosis, Crohn’s disease, diabetes, ulcerative colitis, osteoporosis, transplant rejection, cachexia, cancer, sepsis, memory disorders, atherosclerosis and AIDS. Other exemplified benzoylpyridazines include the following:



Compound	R1	R2	R3	R4	Formula
323704	Me	OEt	H	NH ₂	C ₂₄ H ₃₁ N ₃ O ₅
323705	Me	OEt	H	OCH ₂ CO ₂ H	C ₂₆ H ₃₂ N ₂ O ₈
323706	Me	OMe	H	OH	C ₂₃ H ₂₈ N ₂ O ₆
323707	-CH ₂ O-	H	H	1-Piz-CH ₂ CH ₂ O	C ₂₈ H ₃₆ N ₄ O ₆
323708	Me	H	OMe	OCH ₂ CO ₂ H	C ₂₅ H ₃₀ N ₂ O ₈



Compound	R1	R2	R3	R4	Formula
323709	H	OMe	H	Cl	C ₂₁ H ₂₃ ClN ₂ O ₄
323710	H	H	OEt	OCH ₂ CH ₂ OH	C ₂₄ H ₃₀ N ₂ O ₆
323711	Me	H	OEt	1-Piz-CH ₂ CH ₂ OCH ₂ CH ₂ O	C ₃₁ H ₄₄ N ₄ O ₆

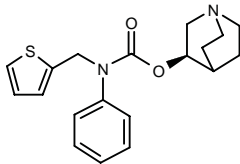
SOURCE – Merck KGaA.

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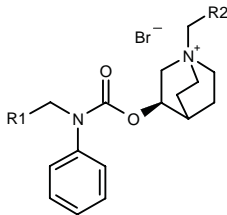
323822

N-Phenyl-N-(thien-2-ylmethyl)carbamic acid 1-azabicyclo-[2.2.2]oct-3(R)-yl ester

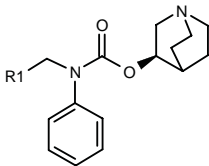


C19 H22 N2 O2 S; Mol wt: 342.4608

ACTION – Muscarinic M₃ receptor antagonist (IC₅₀ = 4.5 nM) for the treatment of respiratory, gastrointestinal or urinary diseases. Compound is reported to show bronchodilating activity and a long duration of action in a bronchospasm model in guinea pigs. Other exemplified quinuclidine carbamate derivatives are:



Compound	R1	R2	Formula
323824	Ph	CH ₂ CH ₂ Ph	C ₃₀ H ₃₅ BrN ₂ O ₂
323825	Ph	CH ₂ OPh	C ₂₉ H ₃₃ BrN ₂ O ₃
323826	Pr	CH=CHPh	C ₂₇ H ₃₅ BrN ₂ O ₂
323827	2-thienyl	2-thienyl-CH ₂ CH ₂	C ₂₆ H ₃₁ BrN ₂ O ₂ S ₂
323828	2-thienyl	CH ₂ OPh	C ₂₇ H ₃₁ BrN ₂ O ₃ S
323830	3-thienyl	CH ₂ OPh	C ₂₇ H ₃₁ BrN ₂ O ₃ S



Compound	R1	Formula
323823	Ph	C ₂₁ H ₂₄ N ₂ O ₂
323829	3-thienyl	C ₁₉ H ₂₂ N ₂ O ₂ S
323831	2-furyl	C ₁₉ H ₂₂ N ₂ O ₃

SOURCE – Almirall Prodesfarma.

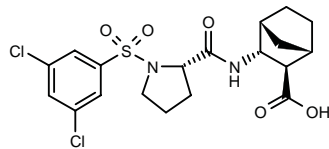
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324064

3*endo*-[1-(3,5-Dichlorophenylsulfonyl)pyrrolidin-2(*S*)-ylcarboxamido]bicyclo[2.2.1]heptane-2*exo*-carboxylic acid

N-(2*exo*-Carboxybicyclo[2.2.1]heptan-3*endo*-yl)-1-(3,5-dichlorophenylsulfonyl)-L-prolinamide



C19 H22 Cl2 N2 O5 S; Mol wt: 461.3638

ACTION – Integrin VLA-4 (very late antigen 4, $\alpha_4\beta_1$) antagonist with nanomolar affinity for VLA-4 (IC_{50} = 54 nM) and high selectivity over integrin $\alpha_4\beta_7$ (IC_{50} = 13 μ M). It exhibited an excellent pharmacokinetic profile in rats, with an oral bioavailability of 49%. Potentially useful for the treatment of inflammatory and autoimmune diseases including asthma, multiple sclerosis and Crohn’s disease.

SOURCE – Merck & Co.

REFERENCES

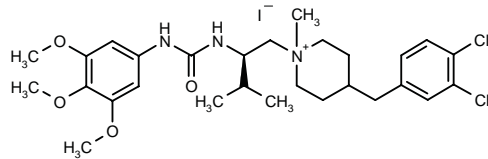
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RO-1169132/238^{2,4}

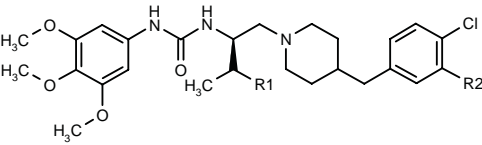
322457

4-(3,4-Dichlorobenzyl)-1-methyl-1-[3-methyl-2(*R*)-[3-(3,4,5-trimethoxyphenyl)ureido]butyl]piperidinium iodide

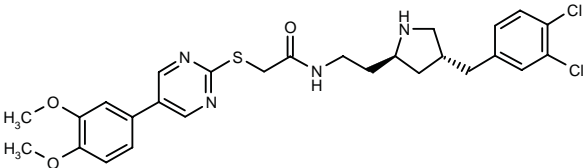


C28 H40 Cl2 I N3 O4; Mol wt: 680.4470

ACTION – Chemokine CCR3 receptor antagonist able to inhibit eotaxin-induced eosinophil shape change in human whole blood (IC_{50} = 7 nM), as well as [¹²⁵I]-eotaxin binding in CCR3 receptor-transfected cells (IC_{50} = 1 nM). It also inhibited eotaxin-induced chemotaxis of L1.2 cells transfected with CCR3 receptors or human eosinophils (IC_{50} = 1.1 and 0.4 nM, respectively). Moreover, it inhibited eotaxin-induced eosinophil CD11b expression and eosinophil and basophil CCR3 internalization, whereas it was not effective against CD11b upregulation on IL-8-stimulated neutrophils or MCP-1-stimulated monocytes. Potentially useful for the treatment of allergic diseases such as asthma. Other related compounds are:



Compound	R1	R2	Formula
Ro-1164875/608 [319655] ^{1,2,4-6}	Me	Cl	C ₂₇ H ₃₇ Cl ₂ N ₃ O ₄
Ro-320947/001 [319656] ^{4,5,7}	OH	H	C ₂₆ H ₃₆ ClN ₃ O ₅



Ro-3300802/001 [322461]^{3,4}: C27 H30 Cl2 N4 O3 S

SOURCE – Roche Bioscience.

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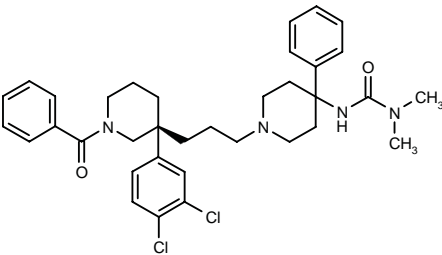
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SSR-146977*

288973

N-[1-[3-[1-Benzoyl-3(*R*)-(3,4-dichlorophenyl)piperidin-3-yl]propyl]-4-phenylpiperidin-4-yl]-*N*',*N*'-dimethylurea



C35 H42 Cl2 N4 O2; Mol wt: 621.6488

ACTION – Potent and selective, nonpeptide tachykinin NK₃ receptor antagonist with high affinity for the human NK₃ receptor ($K_i = 0.26$ nM) and high selectivity over NK₁ and NK₂ receptors. Compound exhibited potent antagonist activity at the NK₃ receptor in a variety of functional assays: it inhibited senktide-induced inositol monophosphate formation ($IC_{50} = 7.8$ -13 nM) and intracellular calcium mobilization ($IC_{50} = 10$ nM) in CHO cells expressing the human NK₃ receptor, antagonized [MePhe⁷]-neurokinin B-induced guinea pig ileum contractions ($pA_2 = 9.07$), and blocked the senktide-induced increase in noradrenergic and dopaminergic neuronal firing rates in guinea pig brain (50-100 nM). In guinea pigs, compound (0.03-1 mg/kg i.p.) inhibited the bronchial hyperresponsiveness to acetylcholine, the histamine-induced increase in bronchial plasma extravasation and citric acid-induced cough. It also inhibited senktide-induced turning behavior ($ID_{50} = 0.2$ mg/kg i.p., 0.4 mg/kg p.o.) and the senktide-induced decrease in locomotor activity (10 and 30 mg/kg i.p.) in gerbils; in guinea pigs, it antagonized senktide-induced acetylcholine release in the hippocampus and norepinephrine release in the prefrontal cortex at doses of 0.3-1 mg/kg i.p. The haloperidol-induced increase in the number of spontaneously active dopamine A10 neurons was also inhibited by compound at doses of 1 and 3 mg/kg i.p. Potentially useful for the treatment of airways inflammation and psychiatric disorders.

SOURCE – Sanofi-Synthelabo.

REFERENCES

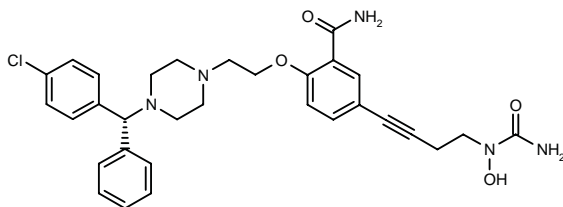
1. Aulombard, A. et al. (Sanofi-Synthelabo) *Ureidopiperidine derivs. as selective human NK3 receptor antagonists*. EP 1119552, WO 0021931.
2. Emonds-Alt, X. et al. *Biochemical and pharmacological activities of SSR 146977, a new potent nonpeptide tachykinin NK3 receptor antagonist*. Can J Physiol Pharmacol 2002, 80(5): 482.
3. *Sanofi-Synthelabo presents overhauled R&D portfolio to financial analysis*. DailyDrugNews.com (Daily Essentials) 2000, March 21.

*Identified compound **288973** Drug Data Rep 2000, 022(08): 0693.

UCB-35440

321317

5-[4-(*N*-Carbamoyl-*N*-hydroxyamino)-1-butynyl]-2-[2-[4-[1(*R*)-(4-chlorophenyl)-1-phenylmethyl]piperazin-1-yl]ethoxy]benzamide



C31 H34 Cl N5 O4; Mol wt: 576.0936

ACTION – Dual-acting 5-lipoxygenase inhibitor and histamine H₁ antagonist with IC_{50} values of 100-180 nM for inhibition 5-lipoxygenase and a K_i value of 110 nM for affinity to human H₁ receptors. Compound inhibited calcium ionophore A-23187-induced LTB₄ production in human whole blood with an IC_{50} value of 109 nM. In ovalbumin-sensitized guinea pigs, doses of 2 and 5 mg/kg p.o. inhibited antigen-induced bronchoconstriction; at the higher dose the effect lasted up to 24 h. Moreover, a dose of 2 mg/kg inhibited histamine-induced bronchoconstriction, as well as *ex vivo* LTB₄ production. Compound is undergoing early clinical trials for the treatment of airways allergies including asthma.

SOURCE – UCB.

REFERENCES

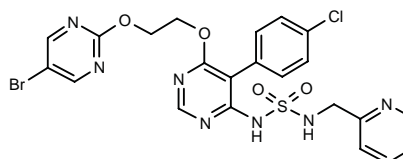
1. Scannel, R. et al. (UCB SA) *Cpds. and methods for treatment of asthma, allergy and inflammatory disorders*. US 6451801, WO 0058295.
2. Cai, X. et al. *Discovery of UCB 35440: A potent and orally active dual acting 5-lipoxygenase inhibitor and H1 receptor antagonist*. 224th ACS Natl Meet (Aug 18-22, Boston) 2002, Abst MEDI 317.
3. Scannell, R.T. et al. *The design and synthesis of a novel series of dual acting molecules possessing 5-lipoxygenase enzyme inhibition and histamine H1 receptor antagonist properties*. Drugs Fut 2002, 27(Suppl. A): Abst C56.
4. *UCB presents R&D overview*. DailyDrugNews.com (Daily Essentials) 2002, June 21.

CARDIOVASCULAR DRUGS

ANTIHYPERTENSIVE DRUGS

324227

N-[6-[2-(5-Bromopyrimidin-2-yloxy)ethoxy]-5-(4-chlorophenyl)pyrimidin-4-yl]-*N'*-(pyridin-2-ylmethyl)sulfamide



C22 H19 Br Cl N7 O4 S; Mol wt: 592.8601

ACTION – Endothelin receptor antagonist with selectivity for endothelin ET_A receptors. This compound exhibited IC_{50} values of 8.5 and 3333 nM for inhibition of endothelin binding to ET_A and ET_B receptors, respectively and inhibited endothelin-induced contractions in isolated rat aorta rings (EA receptors) with a pA_2 value of 8.15 versus a pA_2 value < 5 in rat tracheal rings (ET_B receptors). Potentially useful for the treatment of circulatory disorders such as hypertension, ischemia, vasospasm and angina pectoris, as well as proliferative disorders such as cancer. Other exemplified sulfamides are:

ACTION – Potent and selective, nonpeptide tachykinin NK₃ receptor antagonist with high affinity for the human NK₃ receptor ($K_i = 0.26$ nM) and high selectivity over NK₁ and NK₂ receptors. Compound exhibited potent antagonist activity at the NK₃ receptor in a variety of functional assays: it inhibited senktide-induced inositol monophosphate formation ($IC_{50} = 7.8$ -13 nM) and intracellular calcium mobilization ($IC_{50} = 10$ nM) in CHO cells expressing the human NK₃ receptor, antagonized [MePhe⁷]-neurokinin B-induced guinea pig ileum contractions ($pA_2 = 9.07$), and blocked the senktide-induced increase in noradrenergic and dopaminergic neuronal firing rates in guinea pig brain (50-100 nM). In guinea pigs, compound (0.03-1 mg/kg i.p.) inhibited the bronchial hyperresponsiveness to acetylcholine, the histamine-induced increase in bronchial plasma extravasation and citric acid-induced cough. It also inhibited senktide-induced turning behavior ($ID_{50} = 0.2$ mg/kg i.p., 0.4 mg/kg p.o.) and the senktide-induced decrease in locomotor activity (10 and 30 mg/kg i.p.) in gerbils; in guinea pigs, it antagonized senktide-induced acetylcholine release in the hippocampus and norepinephrine release in the prefrontal cortex at doses of 0.3-1 mg/kg i.p. The haloperidol-induced increase in the number of spontaneously active dopamine A10 neurons was also inhibited by compound at doses of 1 and 3 mg/kg i.p. Potentially useful for the treatment of airways inflammation and psychiatric disorders.

SOURCE – Sanofi-Synthelabo.

REFERENCES

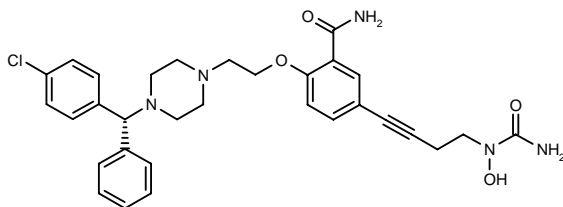
1. Aulombard, A. et al. (Sanofi-Synthelabo) *Ureidopiperidine derivs. as selective human NK3 receptor antagonists*. EP 1119552, WO 0021931.
2. Emonds-Alt, X. et al. *Biochemical and pharmacological activities of SSR 146977, a new potent nonpeptide tachykinin NK3 receptor antagonist*. Can J Physiol Pharmacol 2002, 80(5): 482.
3. *Sanofi-Synthelabo presents overhauled R&D portfolio to financial analysis*. DailyDrugNews.com (Daily Essentials) 2000, March 21.

*Identified compound **288973** Drug Data Rep 2000, 022(08): 0693.

UCB-35440

321317

5-[4-(*N*-Carbamoyl-*N*-hydroxyamino)-1-butynyl]-2-[2-[4-[1(*R*)-(4-chlorophenyl)-1-phenylmethyl]piperazin-1-yl]ethoxy]benzamide



C31 H34 Cl N5 O4; Mol wt: 576.0936

ACTION – Dual-acting 5-lipoxygenase inhibitor and histamine H₁ antagonist with IC_{50} values of 100-180 nM for inhibition 5-lipoxygenase and a K_i value of 110 nM for affinity to human H₁ receptors. Compound inhibited calcium ionophore A-23187-induced LTB₄ production in human whole blood with an IC_{50} value of 109 nM. In ovalbumin-sensitized guinea pigs, doses of 2 and 5 mg/kg p.o. inhibited antigen-induced bronchoconstriction; at the higher dose the effect lasted up to 24 h. Moreover, a dose of 2 mg/kg inhibited histamine-induced bronchoconstriction, as well as *ex vivo* LTB₄ production. Compound is undergoing early clinical trials for the treatment of airways allergies including asthma.

SOURCE – UCB.

REFERENCES

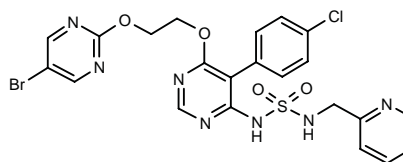
1. Scannel, R. et al. (UCB SA) *Cpds. and methods for treatment of asthma, allergy and inflammatory disorders*. US 6451801, WO 0058295.
2. Cai, X. et al. *Discovery of UCB 35440: A potent and orally active dual acting 5-lipoxygenase inhibitor and H1 receptor antagonist*. 224th ACS Natl Meet (Aug 18-22, Boston) 2002, Abst MEDI 317.
3. Scannell, R.T. et al. *The design and synthesis of a novel series of dual acting molecules possessing 5-lipoxygenase enzyme inhibition and histamine H1 receptor antagonist properties*. Drugs Fut 2002, 27(Suppl. A): Abst C56.
4. *UCB presents R&D overview*. DailyDrugNews.com (Daily Essentials) 2002, June 21.

CARDIOVASCULAR DRUGS

ANTIHYPERTENSIVE DRUGS

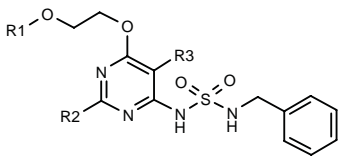
324227

N-[6-[2-(5-Bromopyrimidin-2-yloxy)ethoxy]-5-(4-chlorophenyl)pyrimidin-4-yl]-*N'*-(pyridin-2-ylmethyl)sulfamide



C22 H19 Br Cl N7 O4 S; Mol wt: 592.8601

ACTION – Endothelin receptor antagonist with selectivity for endothelin ET_A receptors. This compound exhibited IC_{50} values of 8.5 and 3333 nM for inhibition of endothelin binding to ET_A and ET_B receptors, respectively and inhibited endothelin-induced contractions in isolated rat aorta rings (EA receptors) with a pA_2 value of 8.15 versus a pA_2 value < 5 in rat tracheal rings (ET_B receptors). Potentially useful for the treatment of circulatory disorders such as hypertension, ischemia, vasospasm and angina pectoris, as well as proliferative disorders such as cancer. Other exemplified sulfamides are:



Compound	R1	R2	R3	Formula
324228	5-Br-2-pyrimidinyl	H	4-Cl-Ph	C ₂₃ H ₂₀ BrClN ₆ O ₄ S
324229	5-(SMe)-2-pyrimidinyl	H	4-Br-Ph	C ₂₄ H ₂₃ BrN ₆ O ₄ S ₂
324231	H	SMe	2-MeO-PhO	C ₂₁ H ₂₄ N ₄ O ₆ S ₂

SOURCE – Actelion.

REFERENCES

1. Bolli, M. et al. (Actelion Ltd.) *Novel sulfamides and their use as endothelin receptor antagonists*. WO 0253557.

ENALAPRIL MALEATE/ NITRENDIPINE

New combination

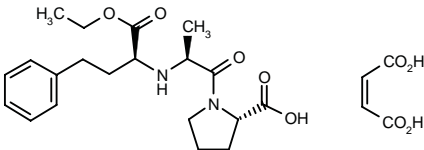
286729

Fixed-dose combination of enalapril maleate and nitrendipine

ENALAPRIL MALEATE

132957

(S)-1-[N-[1-(Ethoxycarbonyl)-3-phenylpropyl]-L-alanyl]-L-proline maleate

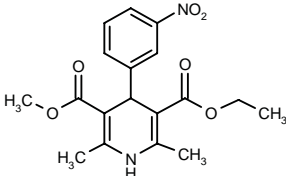


C20 H28 N2 O5 . C4 H4 O4 ; Mol wt: 492.5218

NITRENDIPINE

115055

(±)-2,6-Dimethyl-4-(4-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid ethyl methyl diester



C18 H20 N2 O6; Mol wt: 360.3640

ACTION – Fixed-dose combination of the angiotensin-converting enzyme (ACE) inhibitor enalapril maleate and the calcium channel blocker nitrendipine.

INDICATION – Treatment of essential hypertension in patients not responding to monotherapy with either enalapril or nitrendipine.

PRESENTATION – Tablets, 10 mg enalapril maleate and 20 mg nitrendipine.

PROPRIETARY NAME – Eneas (ES).

SOURCE – Vita-Invest.

SELECTED REFERENCES

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2. Roca-Cusachs, A. et al. *Efficacy of a fixed dose combination of enalapril/ nitrendipine in patients not controlled with enalapril or nitrendipine monotherapy. Results of pooled analysis of two studies: ENEAS-1 and ENEAS-2*. Am J Hypertens 2002, 15(4, Part 2): Abst P-41.

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6. *Licensing opportunity from Vita-Invest: fixed-dose antihypertensive combination*. DailyDrugNews.com (Daily Essentials) 2000, March 20.

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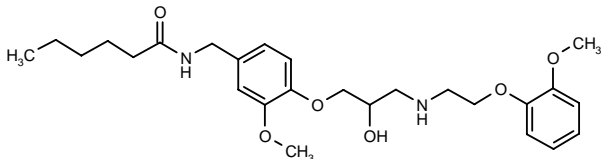
8. *Vita launches Eneas in Spain*. DailyDrugNews.com (Daily Essentials) 2002, July 29.

9. *Vita-Invest's combination therapy for hypertension completes phase III*. DailyDrugNews.com (Daily Essentials) 2001, Feb 23.

KMUP-880708

321792

N-[4-[2-Hydroxy-3-[2-(2-methoxyphenoxy)ethylamino]propoxy]-3-methoxybenzyl]hexanamide



C26 H38 N2 O6; Mol wt: 474.5942

ACTION – Dual α - and β -adrenoceptor antagonist with good affinity and selectivity for cardiac β_1 -adrenoceptors ($pK_i = 7.27$) over lung β_2 -adrenoceptors ($pK_i = 6.08$), and good affinity for brain α -adrenoceptors ($pK_i = 8.25$) in radioligand binding assays. In isolated guinea pig tissues, compound exhibited β -adrenoceptor-antagonist activity, with high selectivity for β_1 -adrenoceptors ($pA_2 = 7.82$ and 7.51 for inhibition of the isoproterenol-induced positive chronotropic and positive inotropic response, respectively, in isolated atrial strips) over β_2 -adrenoceptors ($pA_2 = 6.24$ for inhibition of isoproterenol-induced relaxation of tracheal strips). α -Adrenergic antagonism was observed in rat aorta, where it antagonized noradrenaline-induced vasoconstriction with a pA_2 value of 7.92 . Compound also showed endothelium-independent and K^+ channel opening-associated vasorelaxant activity. It dose-dependently (0.1 - 2.0 mg/kg i.v.) reduced mean blood pressure and heart rate in anesthetized rats, antagonized isoproterenol-induced tachycardia in ganglion-blocked anesthetized rats (0.5 - 2.0 mg/kg i.v.) and antagonized the isoproterenol-induced tachycardia and phenylephrine-induced hypertension in reserpine-treated rats (0.5 - 2.0 mg/kg). Potentially useful for the treatment of hypertension.

SOURCE – Kaohsiung Medical College, Kaohsiung (TW).

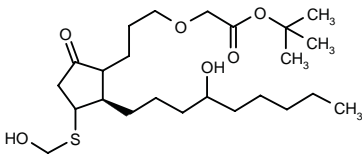
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TREATMENT OF DISORDERS OF THE CORONARY ARTERIES AND ATHEROSCLEROSIS

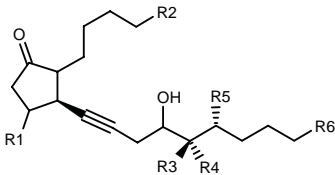
322421

2-[3-[3-(Hydroxymethylsulfanyl)-2(*R*)-(4-hydroxynonyl)-5-oxocyclopentyl]propoxy]acetic acid *tert*-butyl ester

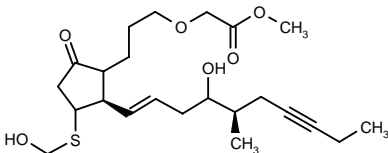


C24 H44 O6 S; Mol wt: 460.6716

ACTION – Prostaglandin analogue with the ability to inhibit the proliferation of vascular smooth muscle cells, potentially useful for the treatment of restenosis following PTCA. Other exemplified compounds include the following:



Compound	R1	R2	R3	R4	R5	R6	Formula
322423	SCH2CH2OH	CH2CH2CO2Me	H	H	Me	Me	C ₂₆ H ₄₄ O ₅ S
322424	SOH	CH2CO2H	H	H	Me	i-Pr	C ₂₄ H ₄₀ O ₅ S
322425	SCH2CH2OH	OCH2CO2Me	Me	H	H	Me	C ₂₅ H ₄₂ O ₆ S
322426	SCH2CH2OH	OCH2CO2H	H	Me	H	Me	C ₂₄ H ₄₀ O ₆ S
322427	SCH2CH2OH	OCH2CO2Me	H	Me	H	Me	C ₂₅ H ₄₂ O ₆ S
322428	SOCH2CH2OH	OCH2CO2Me	Me	H	H	Me	C ₂₅ H ₄₂ O ₇ S
322429	SO2(CH2)3OH	SO2CH2CO2H	H	H	H	H	C ₂₃ H ₃₈ O ₉ S ₂



322422: C23 H36 O6 S

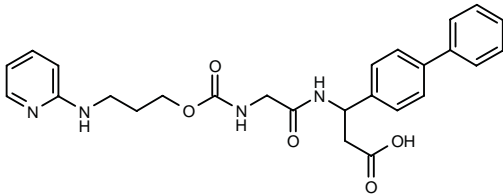
SOURCE – Taisho.

REFERENCES

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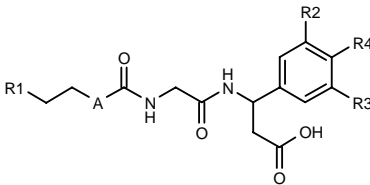
323366

3-(4-Biphenyl)-3-[2-[3-(pyridin-2-ylamino)propoxy-carbonylamino]acetamido]propionic acid



C26 H28 N4 O5; Mol wt: 476.5302

ACTION – Compound with the ability to inhibit the interaction of $\alpha_v\beta_3$ and/or $\alpha_v\beta_6$ integrin receptors with their ligands, potentially useful for the treatment of thrombosis, myocardial infarction, coronary heart disease, arteriosclerosis, inflammation, cancer, osteoporosis, infections, rheumatoid arthritis, diabetic retinopathy and postangioplasty restenosis. Other exemplified compounds are:



Compound	R1	R2=R3	R4	A	Isomer	Formula
323367	2-Pyr-NH	H	3-Cl-Ph	O		C ₂₅ H ₂₅ ClN ₄ O ₅
323368	2-Pyr-NH	H	3-F-Ph	O		C ₂₅ H ₂₅ FN ₄ O ₅
323369	2-Pyr-NH	H	4-Me-Ph	O		C ₂₆ H ₂₈ N ₄ O ₅
323371	2-Pyr-NH	H	4-CF3-Ph	O		C ₂₆ H ₂₅ F ₃ N ₄ O ₅
323372	2-Pyr-NH	H	Ph	O	R	C ₂₅ H ₂₆ N ₄ O ₅
323373	2-Pyr-NH	Cl	H	O		C ₁₉ H ₂₀ Cl ₂ N ₄ O ₅
323374	2-benzimidazolyl-NH	H	Ph	NH		C ₂₇ H ₂₈ N ₆ O ₄
323375	2-Pyr-NHCH2	H	4-Cl-Ph	NH		C ₂₆ H ₂₈ ClN ₅ O ₄

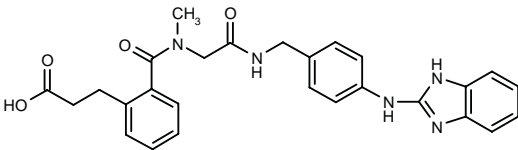
SOURCE – Merck KGaA.

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323626

3-[2-[*N*-[*N*-[4-(1*H*-Benzimidazol-2-ylamino)benzyl]-carbamoylmethyl]-*N*-methylcarbamoyl]phenyl]propionic acid



C27 H27 N5 O4; Mol wt: 485.5413

ACTION – A representative compound from a series of modulators of integrin $\alpha_v\beta_3$ receptors, potentially useful for the treatment of myocardial infarction, stroke, congestive heart failure, restenosis, diabetic angiopathy, atherosclerosis, cancer, osteoporosis, rheumatoid arthritis and wound healing.

SOURCE – Abbott.

REFERENCES

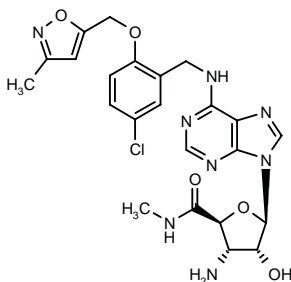
1. Geneste, H. et al. (Abbott GmbH & Co. KG) *Integrin receptor ligands*. DE 10064823, WO 0251810.

CP-608039*

303352

3(S)-Amino-5(R)-[N⁶-[5-chloro-2-(3-methylisoxazol-5-ylmethoxy)benzyl]adenin-9-yl]-4(R)-hydroxy-N-methyltetrahydrofuran-2(S)-carboxamide

3-Amino-1-[N⁶-[5-chloro-2-(3-methylisoxazol-5-ylmethoxy)benzyl]adenin-9-yl]-1,3-dideoxy-N-methyl- β -D-ribofuranuronamide



C23 H25 Cl N8 O5; Mol wt: 528.9545

ACTION – Adenosine A₃ receptor agonist (K_i = 5.8 nM) with > 1,000-fold selectivity over A₁ receptors and an EC₅₀ value of 3 nM in functional assays. Selected as a clinical candidate for the treatment of perioperative ischemic injury.

SOURCE – Pfizer.

REFERENCES

1. Masamune, H. et al. (Pfizer Products Inc.) *Cpds. for the treatment of ischemia*. EP 1216257, WO 0123399.
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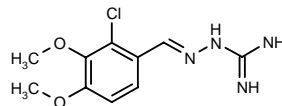
*Identified compound **303352** (see **303348**) Drug Data Rep 2001, 023(08): 0767.

ME-10092

301845

N¹-(2-Chloro-3,4-dimethoxybenzylideneamino)guanidine

PR-9



C10 H13 Cl N4 O2; Mol wt: 256.6917

ACTION – Antioxidant proven to protect tissues from ischemia/reperfusion injury and to reduce myocardial infarct size in a pig model. In pigs subjected to myocardial ischemia (60 min) followed by reperfusion (120 min), a dose of 2 mg/kg given into the left atrium 5 min before reperfusion produced a significant reduction in myocardial infarct size of 25% compared to controls; a higher dose of 10 mg/kg produced a nonsignificant reduction in infarct size. Moreover, compound has been found to protect animals from the arrhythmia burst and mortality associated with reperfusion injury. Potentially useful for the treatment of myocardial infarction.

SOURCE – Melacure Therapeutics.

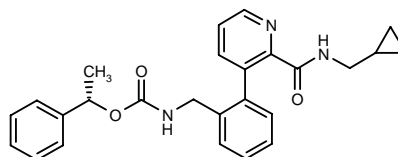
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2. Pett, C.P. et al. (Melacure Therapeutics) *Guanidine derivs. and their use in the production of a medicament for blocking xanthine oxidase/dehydrogenase*. WO 0125192.
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4. Dambrova, M. et al. *The novel guanidine ME10092 protects the heart during ischemia-reperfusion*. Eur J Pharmacol 2002, 445(1-2): 105.
5. Kavianipour, M. et al. *ME10092 a novel antioxidant reduces myocardial infarct size in a porcine in vivo model*. Cardiovasc Drugs Ther 2001, 15(Suppl. 1): Abst P081.
6. Kavianipour, M. et al. *ME10092 a novel antioxidant reduces myocardial infarct size in a porcine in vivo model*. Eur Heart J 2001, 22(Suppl.): Abst P3618.

ANTIARRHYTHMIC DRUGS

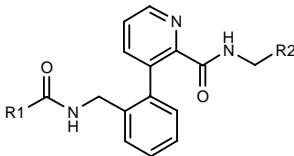
322765

N-[2-[2-[N-(Cyclopropylmethyl)carbamoyl]pyridin-3-yl]benzyl]carbamic acid 1(S)-phenylethyl ester



C26 H27 N3 O3; Mol wt: 429.5173

ACTION – Inhibitor of Kv1.5 potassium channels, as demonstrated by inhibition of ion currents through the human Kv1.5 channel expressed in *Xenopus* oocytes (IC_{50} = 0.4 μ M). Potentially useful for the treatment of atrial arrhythmia, i.e., atrial fibrillation and atrial flutter. Other exemplified bisaryl carboxamide derivatives are:



Compound	R1	R2	Formula
322767	(S)-OCH(Me)Ph	2-Pyr-CH2	C ₂₉ H ₂₈ N ₄ O ₃
322768	(S)-OCH(Me)Ph	3-Pyr	C ₂₈ H ₂₆ N ₄ O ₃
322769	(R)-CH2CH(Me)Ph	cyclopropyl	C ₂₇ H ₂₈ N ₃ O ₂
322770	4-F-PhCH(Me)CH2	2-Pyr-CH2	C ₃₀ H ₂₉ FN ₄ O ₂
322771	(R)-CH2CH(Me)Ph	2-Pyr-CH2	C ₃₀ H ₃₀ N ₄ O ₂
322772	(S)-OCH(Me)Ph	3-Pyr-CH2	C ₂₉ H ₂₈ N ₄ O ₃
322773	4-Cl-PhC(Me)2	2-Pyr-CH2	C ₃₀ H ₂₉ ClN ₄ O ₂

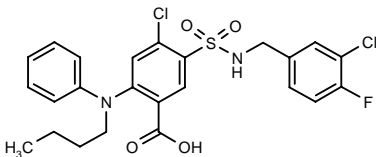
SOURCE – Aventis Pharma.

REFERENCES

1. Peukert, S. et al. (Aventis Pharma Deutschland GmbH) *Ortho-substd. nitrogen-containing bisaryl cpds. used as potassium channel inhibitors*. DE 10060807, WO 0246162.

322854

2-(*N*-Butyl-*N*-phenylamino)-4-chloro-5-[*N*-(3-chloro-4-fluorobenzyl)sulfamoyl]benzoic acid



C24 H23 Cl2 F N2 O4 S; Mol wt: 525.4257

ACTION – A representative compound from a series of 2-amino-5-sulfamoylbenzoic acid derivatives able to inhibit the cellular Na^+/HCO_3^- cotransporter (NBC; 54% at 10 μ M). Potentially useful for the treatment of arrhythmia, myocardial infarction, angina pectoris, ischemic disorders of the heart, central and peripheral nervous system and organs, shock and proliferative disorders, as well as for the preservation of organs for transplantation.

SOURCE – Aventis Pharma.

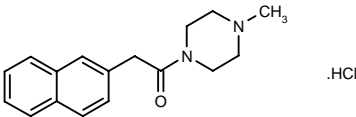
REFERENCES

1. Weichert, A. et al. (Aventis Pharma Deutschland GmbH) *Substd. anthranilic acids*. DE 10060809, WO 0246148.

RSD-992

243596

1-(4-Methylpiperazin-1-yl)-2-(2-naphthyl)ethanone hydrochloride



C17 H20 N2 O . HCl; Mol wt: 304.8189

ACTION – Antiarrhythmic agent, a sodium channel blocker selective for rat cardiac Na^+ (rNav1.5) channels over neuronal Na^+ (rNav1.2a) channels expressed in *Xenopus* oocytes. In rats with coronary artery occlusion, compound (2-24 μ mol/kg/min i.v.) decreased the incidence of ventricular arrhythmia and mortality. This compound was previously described as a stimulant of erectile function in rodents owing to its 5-HT-agonist activity.

SOURCES – Cardiome; Xoma.

REFERENCES

1. Hayes, E.S. (Nortran Pharmaceuticals, Inc.) *Serotonin ligands as pro-erectile cpds*. WO 0028993.

2. Zolotoy, A.B. and Hayes, E.S. (Nortran Pharmaceuticals Inc.) *Aroylpipezazines for modulating sexual activity*. WO 9902159.

3. Hayes, E.S. et al. *Actions of aroylpipezazines on corpus cavernosum smooth muscle in vitro*. Asia Pac J Pharmacol 1997, 12(3): 97.

4. Hayes, E.S. et al. *Pro-erectile effects of novel serotonin agonists*. Int J Impot Res 2000, 12(Suppl. 3): Abst A3.

5. Hayes, E.S. et al. *RSD 992 enhances erection and copulation in rats and erection in primates*. Int J Impot Res 1996, 8(3): Abst P24.

6. Hayes, E.S. et al. *The effects of 5HT agonists on central, peripheral and local erectile pathways*. Int J Impot Res 1997, 9(Suppl. 1): Abst A8.

7. Hayes, E.S. et al. *The effects of novel serotonin agonists on erection and sexual behavior in male rats and monkeys: Potential new therapies for erectile dysfunction*. Int J Impot Res 2001, 13(Suppl. 1): Abst P68.

8. Pugsley, M.K. et al. *A characterization of the antiarrhythmic and electrophysiological properties of RSD992, a novel aroylpipezazine drug*. Pharmacologist 2002, 44(2, Suppl. 1): Abst 22.8.

HEART FAILURE THERAPY

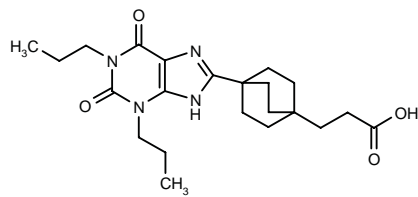
BG-9928

323844

3-[4-(2,6-Dioxo-1,3-dipropyl-2,3,6,9-tetrahydro-1*H*-purin-8-yl)bicyclo[2.2.2]oct-1-yl]propionic acid

3-[4-(1,3-Dipropylxanthin-8-yl)bicyclo[2.2.2]oct-1-yl]-propionic acid

BIO-9002



C22 H32 N4 O4; Mol wt: 416.5188

ACTION – Potent and selective adenosine A₁ antagonist (K_i = 7.4 nM) with good selectivity over A_{2A}, A_{2B} and A₃ receptor subtypes (K_i = 6400, 90 and 17,500 nM, respectively). It showed high water solubility (> 10 mg/ml) and a favorable pharmacokinetic profile in rats, with an oral bioavailability of 99%, a half-life of 4 h and a mean clearance of 1.6 ml/min/h. It was active in a rat model of diuretic-induced renal dysfunction (1 mg/kg i.v.) and in rat and monkey models of myocardial infarction and pulmonary hemodynamic disorder. Results of phase I clinical studies in healthy volunteers showed that a single oral dose of 1 mg/kg was well tolerated, and a half-life of 18 h was measured. Potentially useful for the treatment of heart failure.

SOURCE – Biogen.

REFERENCES

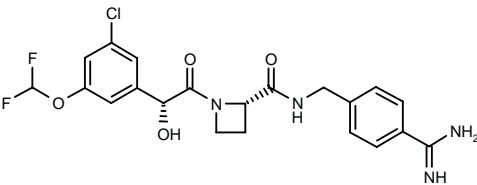
1. Kiesman, W.F. et al. (Biogen, Inc.) *Polycycloalkylpurines as adenosine receptor antagonists*. WO 0134610.
2. Petter, R.C. et al. *Novel adenosine A₁-receptor antagonists*. 224th ACS Natl Meet (Aug 18-22, Boston) 2002, Abst MEDI 417.

AGENTS AFFECTING BLOOD COAGULATION

ANTICOAGULANTS

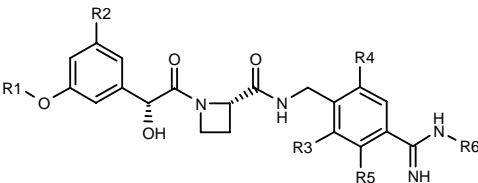
322305

N-(4-Amidinobenzyl)-1-[2(*R*)-[3-chloro-5-(difluoromethoxy)phenyl]-2-hydroxyacetyl]azetidine-2(*S*)-carboxamide



C21 H21 Cl F2 N4 O4; Mol wt: 466.8699

ACTION – Thrombin inhibitor with potential in the treatment of thrombosis and conditions associated with hypercoagulability in blood and tissues. Other exemplified mandelic acid derivatives are:



Compound	R1	R2	R3	R4	R5	R6	Formula
322306	CH(CH ₂ F) ₂	Cl	H	H	H	H	C ₂₃ H ₂₆ ClF ₂ N ₄ O ₄
322307	CHF ₂	F	H	H	H	H	C ₂₁ H ₂₁ F ₃ N ₄ O ₄
322312	CHF ₂	Cl	F	F	H	H	C ₂₁ H ₁₉ ClF ₄ N ₄ O ₄
322313	CHF ₂	Cl	H	H	H	OH	C ₂₁ H ₂₁ ClF ₂ N ₄ O ₅
322315	CF ₃	Cl	H	H	H	cyclohexyl-O	C ₂₇ H ₃₀ ClF ₃ N ₄ O ₅
322316	CF ₃	Cl	H	H	H	2-Br-PhCH ₂ O	C ₂₈ H ₂₆ BrClF ₃ N ₄ O ₅
322317	CHF ₂	F	H	H	H	OMe	C ₂₂ H ₂₃ F ₃ N ₄ O ₅
322318	CHF ₂	Cl	H	F	F	OMe	C ₂₂ H ₂₁ ClF ₄ N ₄ O ₅

SOURCE – AstraZeneca.

REFERENCES

1. Inghardt, T. et al. (AstraZeneca AB) *New mandelic acid derivs. and their use as thrombin inhibitors*. WO 0244145.

HEART FAILURE THERAPY

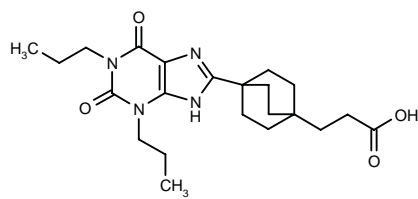
BG-9928

323844

3-[4-(2,6-Dioxo-1,3-dipropyl-2,3,6,9-tetrahydro-1*H*-purin-8-yl)bicyclo[2.2.2]oct-1-yl]propionic acid

3-[4-(1,3-Dipropylxanthin-8-yl)bicyclo[2.2.2]oct-1-yl]-propionic acid

BIO-9002



C22 H32 N4 O4; Mol wt: 416.5188

ACTION – Potent and selective adenosine A₁ antagonist (K_i = 7.4 nM) with good selectivity over A_{2A}, A_{2B} and A₃ receptor subtypes (K_i = 6400, 90 and 17,500 nM, respectively). It showed high water solubility (> 10 mg/ml) and a favorable pharmacokinetic profile in rats, with an oral bioavailability of 99%, a half-life of 4 h and a mean clearance of 1.6 ml/min/h. It was active in a rat model of diuretic-induced renal dysfunction (1 mg/kg i.v.) and in rat and monkey models of myocardial infarction and pulmonary hemodynamic disorder. Results of phase I clinical studies in healthy volunteers showed that a single oral dose of 1 mg/kg was well tolerated, and a half-life of 18 h was measured. Potentially useful for the treatment of heart failure.

SOURCE – Biogen.

REFERENCES

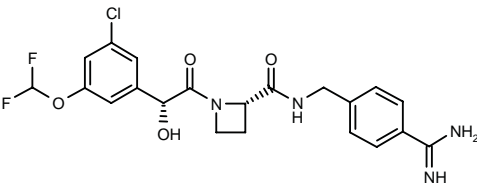
1. Kiesman, W.F. et al. (Biogen, Inc.) *Polycycloalkylpurines as adenosine receptor antagonists*. WO 0134610.
2. Petter, R.C. et al. *Novel adenosine A₁-receptor antagonists*. 224th ACS Natl Meet (Aug 18-22, Boston) 2002, Abst MEDI 417.

AGENTS AFFECTING BLOOD COAGULATION

ANTICOAGULANTS

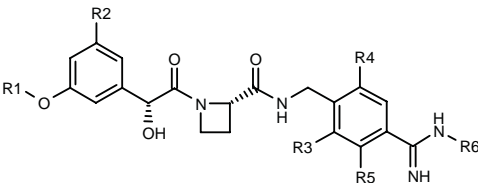
322305

N-(4-Amidinobenzyl)-1-[2(*R*)-[3-chloro-5-(difluoromethoxy)phenyl]-2-hydroxyacetyl]azetidine-2(*S*)-carboxamide



C21 H21 Cl F2 N4 O4; Mol wt: 466.8699

ACTION – Thrombin inhibitor with potential in the treatment of thrombosis and conditions associated with hypercoagulability in blood and tissues. Other exemplified mandelic acid derivatives are:



Compound	R1	R2	R3	R4	R5	R6	Formula
322306	CH(CH ₂ F) ₂	Cl	H	H	H	H	C ₂₃ H ₂₆ ClF ₂ N ₄ O ₄
322307	CHF ₂	F	H	H	H	H	C ₂₁ H ₂₁ F ₃ N ₄ O ₄
322312	CHF ₂	Cl	F	F	H	H	C ₂₁ H ₁₉ ClF ₄ N ₄ O ₄
322313	CHF ₂	Cl	H	H	H	OH	C ₂₁ H ₂₁ ClF ₂ N ₄ O ₅
322315	CF ₃	Cl	H	H	H	cyclohexyl-O	C ₂₇ H ₃₀ ClF ₃ N ₄ O ₅
322316	CF ₃	Cl	H	H	H	2-Br-PhCH ₂ O	C ₂₈ H ₂₆ BrClF ₃ N ₄ O ₅
322317	CHF ₂	F	H	H	H	OMe	C ₂₂ H ₂₃ F ₃ N ₄ O ₅
322318	CHF ₂	Cl	H	F	F	OMe	C ₂₂ H ₂₁ ClF ₄ N ₄ O ₅

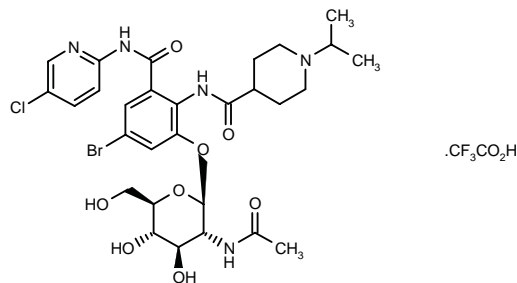
SOURCE – AstraZeneca.

REFERENCES

1. Inghardt, T. et al. (AstraZeneca AB) *New mandelic acid derivs. and their use as thrombin inhibitors*. WO 0244145.

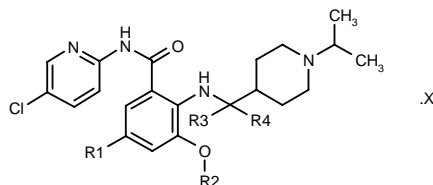
322456

N-[2-(2-Acetamido-2-deoxy-β-D-glucopyranosyloxy)-4-bromo-6-[*N*-(5-chloropyridin-2-yl)carbamoyl]phenyl]-1-iso-propylpiperidine-4-carboxamide trifluoroacetate



C29 H37 Br Cl N5 O8 . C2 H F3 O2; Mol wt: 813.0172

ACTION – Agent with factor X-inhibitory activity that gave a CT2 value (concentration required to double coagulation time) of 0.062 μM when tested in human plasma treated with human factor Xa. In an *ex vivo* assay in monkeys, orally administered compound (10 mg/kg) prolonged the prothrombin time. Potentially useful for the treatment of thrombotic disorders such as cerebral infarction, cerebral thrombosis, transient ischemic attack, myocardial infarction, unstable angina, coronary thrombolysis, pulmonary infarction, pulmonary embolism, peripheral arterial obstruction, deep venous thrombosis and disseminated intravascular coagulation. Other exemplified substituted benzene derivatives are:



Compound	R1	R2	R3	R4	X	Formula
322458	Br	β-D-galactopyranosyl	-O-		CF3CO2H	C ₂₇ H ₃₄ BrClN ₄ O ₈ .C ₂ HF ₃ O ₂
322459	Br	6-O-Me-β-D-glucopyranosyl	-O-		CF3CO2H	C ₂₈ H ₃₆ BrClN ₄ O ₈ .C ₂ HF ₃ O ₂
322460	Cl	H	H	H	HCl	C ₂₁ H ₂₆ Cl ₂ N ₄ O ₂ .HCl
322462	Cl	H	-O-		HCl	C ₂₁ H ₂₄ Cl ₂ N ₄ O ₃ .HCl

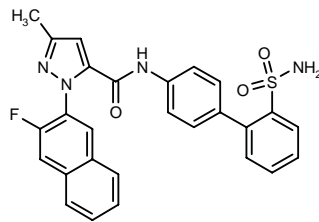
SOURCE – Yamanouchi.

REFERENCES

1. Ishihara, T. et al. (Yamanouchi Pharmaceutical Co., Ltd.) *Substd. benzene derivs. or salts thereof*. WO 0242270.

322877

1-(3-Fluoronaphthalen-2-yl)-3-methyl-*N*-(2'-sulfamoyl-biphenyl-4-yl)-1*H*-pyrazole-5-carboxamide



C27 H21 F N4 O3 S; Mol wt: 500.5519

ACTION – Anticoagulant, a potent inhibitor of coagulation factor Xa (K_i = 5.7 nM, IC_{50} = 9 nM) with high selectivity over thrombin, trypsin, tPA, plasmin and kallikrein (IC_{50} = 11 μM or more). Compound (4 mg/kg in 25% PEG-300) showed discrete oral bioavailability in dogs (22%) and a half-life of 6 h.

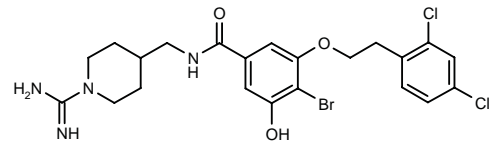
SOURCE – Millennium.

REFERENCES

1. Zhu, B.-Y. et al. (Millennium Pharmaceuticals, Inc.) *Benzamides and related inhibitors of factor Xa*. EP 1216228, EP 1216231, WO 0119788, WO 0119798.
2. Jia, Z.J. et al. *Design, synthesis and biological activity of novel non-amidine factor Xa inhibitors: Part 1: Structure-activity relationships of the substituted 1-(2-naphthyl)-1*H*-pyrazole-5-carboxylamides*. Bioorg Med Chem Lett 2002, 12(12): 1651.

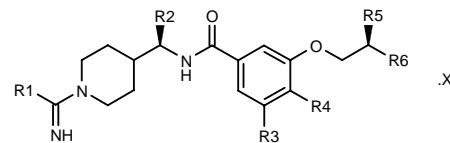
322913

N-(1-Amidinopiperidin-4-ylmethyl)-4-bromo-3-[2-(2,4-dichlorophenyl)ethoxy]-5-hydroxybenzamide



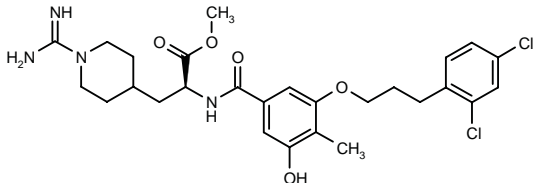
C22 H25 Br Cl2 N4 O3; Mol wt: 544.2745

ACTION – Factor Xa inhibitor (K_i = 0.0137 μM) for use in the treatment of coagulation disorders, inflammation, fibrinolysis, cardiovascular disorders, thromboembolic disorders, restenosis, abnormal thrombus formation, acute myocardial infarction, unstable angina, acute vessel closure associated with thrombolytic therapy, transient ischemic attacks, viral infections, cancer, etc. Other exemplified guanidine and amidine derivatives are:



Compound	R1	R2	R3	R4	R5	R6	X	Formula
322914	NH2	CO2Me	OH	H	H	2,4-(Cl)2-Ph		C ₂₄ H ₂₆ Cl ₂ N ₄ O ₅
322915	NH2	H	OH	Me	H	2,4-(Cl)2-Ph		C ₂₃ H ₂₆ Cl ₂ N ₄ O ₃
322916	NH2	H	OH	H	H	2,4-(Cl)2-Ph		C ₂₂ H ₂₆ Cl ₂ N ₄ O ₃
322917	NH2	CO2Me	OH	H	H	2,4-(Cl)2-PhCH2		C ₂₅ H ₃₀ Cl ₂ N ₄ O ₅
322919	NH2	CO2Me	OH	Me	H	3-NO2-Ph		C ₂₅ H ₃₁ N ₅ O ₇

Compound	R1	R2	R3	R4	R5	R6	X	Formula
322920	NH2	H	OH	Br	NH2	4-Cl-Ph		C ₂₂ H ₂₇ BrClN ₅ O ₃
322921	NH2	H	OH	Me	H	3-Pyr		C ₂₂ H ₂₉ N ₅ O ₃
322922	NH2	H	OH	Br	H	3-Pyr		C ₂₁ H ₂₆ BrN ₅ O ₃
322923	NH2	H	H	OMe	H	2,4-(Cl)2-Ph		C ₂₃ H ₂₈ Cl ₂ N ₄ O ₃
322924	Me	H	H	Me	H	2,4-(Cl)2-Ph	CF ₃ CO ₂ H	C ₂₄ H ₂₉ Cl ₂ N ₃ O ₂ C ₂ HF ₃ O ₂
322925	NH2	H	H	Me	H	2,4-(Cl)2-Ph	CF ₃ CO ₂ H	C ₂₃ H ₂₈ Cl ₂ N ₄ O ₂ C ₂ HF ₃ O ₂



322918: C27 H34 Cl2 N4 O5

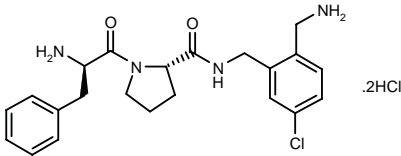
SOURCE – Aventis Pharma.

REFERENCES

1. Peyman, A. et al. (Aventis Pharma Deutschland GmbH) *Guanidine and amidine derivs. as factor Xa inhibitors*. WO 0246159.

323255

D-Phenylalanyl-N-[2-(aminomethyl)-5-chlorobenzyl]-L-prolinamide dihydrochloride



C22 H27 Cl N4 O2 . 2HCl; Mol wt: 487.8561

ACTION – A representative compound from a series of N-benzyl carboxamide compounds that acts as a thrombin inhibitor. Potentially useful for the treatment of venous thromboembolism, pulmonary embolism, deep venous thrombosis and thromboembolic stroke.

SOURCE – Merck & Co.

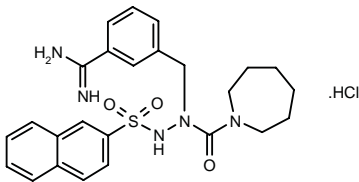
REFERENCES

1. Selnick, H.G. et al. (Merck & Co., Inc.) *Benzylamine derivs. and their use as thrombin inhibitors*. WO 0250056.

323628

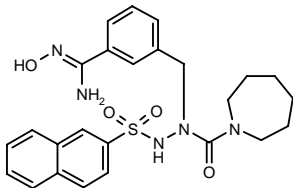
3-[N¹-(Perhydro-1H-azepin-1-ylcarbonyl)-N²-(naphthalen-2-ylsulfonyl)hydrazinomethyl]benzamidine hydrochloride

N²-(3-Amidinophenylmethyl)-N²-(perhydroazepin-1-yl-carbonyl)naphthalene-2-sulfonohydrazide hydrochloride



C25 H29 N5 O3 S . HCl; Mol wt: 516.0630

ACTION – Selective thrombin inhibitor ($K_i = 0.005 \mu\text{M}$) with 29-fold selectivity over trypsin. In a rat model of venous thrombosis induced by tissue factor and stasis, it showed protective effects with an ED_{50} value of 70 mg/kg i.v. The hemorrhagic risk associated with this compound was also determined in the rat tail transection model, where a 9.4-fold increase in bleeding was observed at a dose of 1 mg/kg i.v. Potentially useful for the treatment of thrombotic disorders including venous and arterial thrombosis, pulmonary embolism, cardiogenic thromboembolism, etc. Another exemplified compound is:



323629: C25 H29 N5 O4 S

SOURCES – LEK; University of Ljubljana, Ljubljana (SI).

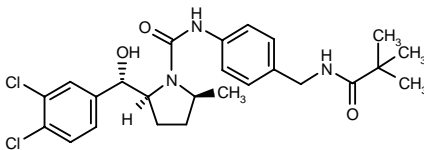
REFERENCES

1. Urleb, U. et al. (University of Ljubljana;LEK Pharmaceutical and Chemical Co.) *Amidinophenylalanine derivs. as thrombin inhibitors*. WO 0251824.

ANTIPLATELET THERAPY

322688

2(S)-[1(S)-(3,4-Dichlorophenyl)-1-hydroxymethyl]-N-[4-(2,2-dimethylpropionamidomethyl)phenyl]-5(S)-methylpyrrolidine-1-carboxamide



C25 H31 Cl2 N3 O3; Mol wt: 492.4439

ACTION – Thrombin receptor antagonist for use in anti-platelet therapy.

SOURCE – Merck & Co.

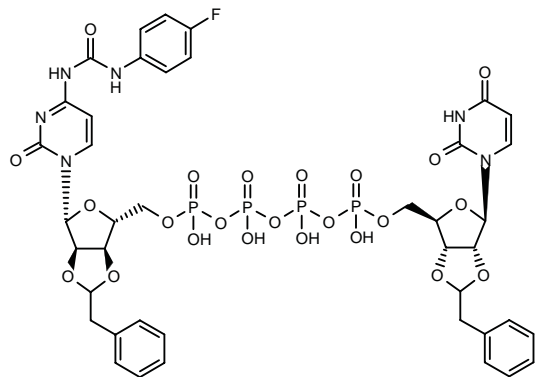
REFERENCES

1. Nantermet, P.G. et al. (Merck & Co., Inc.) *Thrombin receptor antagonists*. US 6403612.

INS-49162

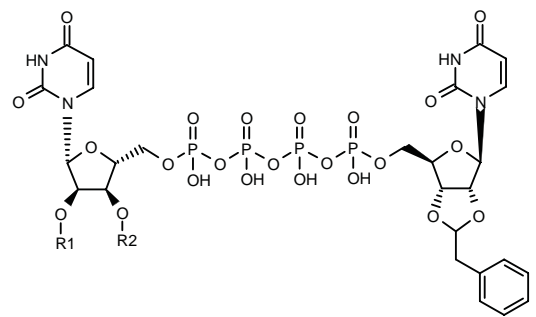
322198

P1-[N⁶-[N-(4-Fluorophenyl)carbamoyl]-2'-O,3'-O-(2-phenylethylidene)cytidin-5'-yl]-P4-[2'-O,3'-O-(2-phenylethylidene)uridin-5'-yl]tetraphosphate



C41 H43 F N6 O23 P4; Mol wt: 1130.7040

ACTION – Antiplatelet agent, a potent and selective human platelet P2Y₁₂ receptor antagonist that inhibited ADP-induced human platelet aggregation in a competitive and reversible manner (IC₅₀ = 170 nM). Compound strongly inhibited *ex vivo* ADP-induced platelet aggregation in mice at a dose of 50 mg/kg i.v., without affecting platelet shape change. Other related compounds are:



Compound	R1	R2	Formula
INS-46059 [322194]	H	H	C ₂₆ H ₃₂ N ₄ O ₂₃ P ₄
INS-46060 [322195]	-CH(CH ₂ Ph)-		C ₃₄ H ₃₈ N ₄ O ₂₃ P ₄

SOURCE – Inspire Pharmaceuticals.

REFERENCES

1. Boyer, J.L. et al. (Inspire Pharmaceuticals, Inc.;University of North Carolina) *Compsn. and method for inhibiting platelet aggregation*. WO 0216381.

2. Boyer, J.L. et al. *Compsn. and method for inhibiting platelet aggregation*. US 2002052337.

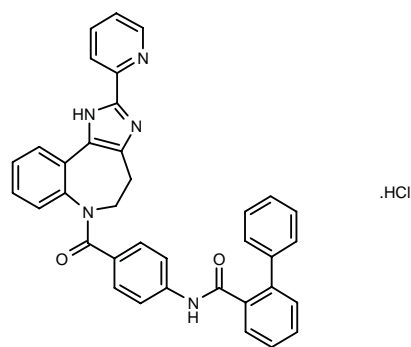
3. Boyer, J.L. et al. *Inhibition of platelet aggregation by novel selective P2Y(12) receptor antagonists*. Pharmacologist 2002, 44(2, Suppl. 1): Abst 146.10.

RENAL–UROLOGIC DRUGS

DIURETICS

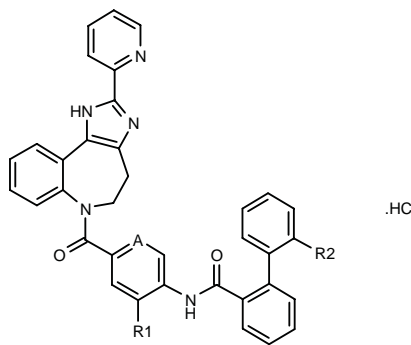
322602

N-[4-[2-(2-Pyridyl)-1,4,5,6-tetrahydroimidazo[4,5-*d*]-1-benzazepin-6-ylcarbonyl]phenyl]biphenyl-2-carboxamide hydrochloride



C36 H27 N5 O2 . HCl; Mol wt: 598.1032

ACTION – Vasopressin V_{1a} and V₂ receptor antagonist that displayed pK_i values of 8.55 and 8.22, respectively, at these receptors. Potentially useful as a diuretic and vasodilator, as well as in the treatment of hypertension, heart failure, renal failure, coagulation disorders, hyponatremia, vasopressin secretion anomaly syndrome, nephropathy, cerebral edema, ascites and hepatic cirrhosis. Other exemplified compounds are:



Compound	R1	R2	A	Formula
322603	H	F	CH	C ₃₆ H ₂₆ FN ₅ O ₂ .HCl
322604	H	H	N	C ₃₅ H ₂₆ N ₆ O ₂ .HCl
322605	OH	H	CH	C ₃₆ H ₂₇ N ₅ O ₃ .HCl

SOURCE – Yamanouchi.

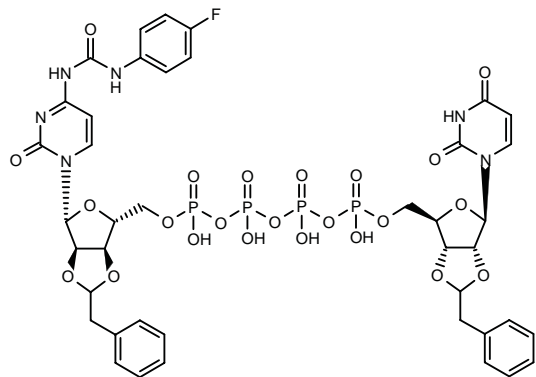
REFERENCES

1. Kakefuda, A. et al. (Yamanouchi Pharmaceutical Co., Ltd.) *1,4,5,6-Tetrahydroimidazo[4,5-d]diazepine derivs. or salts thereof*. WO 0244179.

INS-49162

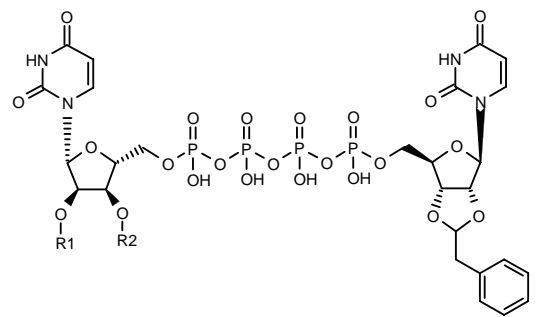
322198

P1-[N⁶-[N-(4-Fluorophenyl)carbamoyl]-2'-O,3'-O-(2-phenylethylidene)cytidin-5'-yl]-P4-[2'-O,3'-O-(2-phenylethylidene)uridin-5'-yl]tetraphosphate



C41 H43 F N6 O23 P4; Mol wt: 1130.7040

ACTION – Antiplatelet agent, a potent and selective human platelet P2Y₁₂ receptor antagonist that inhibited ADP-induced human platelet aggregation in a competitive and reversible manner (IC₅₀ = 170 nM). Compound strongly inhibited *ex vivo* ADP-induced platelet aggregation in mice at a dose of 50 mg/kg i.v., without affecting platelet shape change. Other related compounds are:



Compound	R1	R2	Formula
INS-46059 [322194]	H	H	C ₂₆ H ₃₂ N ₄ O ₂₃ P ₄
INS-46060 [322195]	-CH(CH ₂ Ph)-		C ₃₄ H ₃₈ N ₄ O ₂₃ P ₄

SOURCE – Inspire Pharmaceuticals.

REFERENCES

1. Boyer, J.L. et al. (Inspire Pharmaceuticals, Inc.;University of North Carolina) *Compsn. and method for inhibiting platelet aggregation*. WO 0216381.

2. Boyer, J.L. et al. *Compsn. and method for inhibiting platelet aggregation*. US 2002052337.

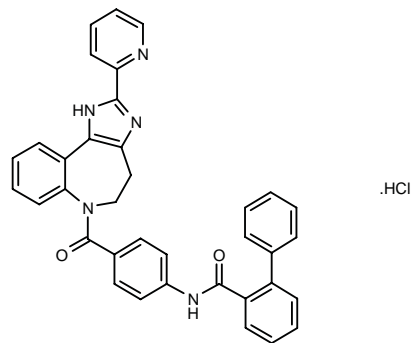
3. Boyer, J.L. et al. *Inhibition of platelet aggregation by novel selective P2Y(12) receptor antagonists*. Pharmacologist 2002, 44(2, Suppl. 1): Abst 146.10.

RENAL–UROLOGIC DRUGS

DIURETICS

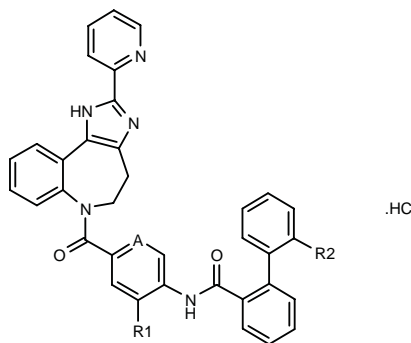
322602

N-[4-[2-(2-Pyridyl)-1,4,5,6-tetrahydroimidazo[4,5-*d*]-1-benzazepin-6-ylcarbonyl]phenyl]biphenyl-2-carboxamide hydrochloride



C36 H27 N5 O2 . HCl; Mol wt: 598.1032

ACTION – Vasopressin V_{1a} and V₂ receptor antagonist that displayed pK_i values of 8.55 and 8.22, respectively, at these receptors. Potentially useful as a diuretic and vasodilator, as well as in the treatment of hypertension, heart failure, renal failure, coagulation disorders, hyponatremia, vasopressin secretion anomaly syndrome, nephropathy, cerebral edema, ascites and hepatic cirrhosis. Other exemplified compounds are:



Compound	R1	R2	A	Formula
322603	H	F	CH	C ₃₆ H ₂₆ FN ₅ O ₂ .HCl
322604	H	H	N	C ₃₅ H ₂₆ N ₆ O ₂ .HCl
322605	OH	H	CH	C ₃₆ H ₂₇ N ₅ O ₃ .HCl

SOURCE – Yamanouchi.

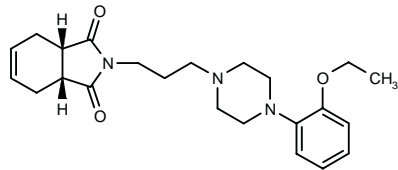
REFERENCES

1. Kakefuda, A. et al. (Yamanouchi Pharmaceutical Co., Ltd.) *1,4,5,6-Tetrahydroimidazo[4,5-d]diazepine derivs. or salts thereof*. WO 0244179.

BENIGN PROSTATIC HYPERPLASIA
THERAPY

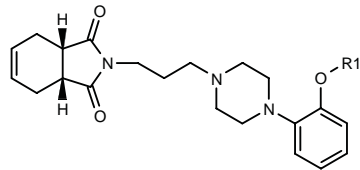
322283

cis-2-[3-[4-(2-Ethoxyphenyl)piperazin-1-yl]propyl]-2,3,3a,4,7,7a-hexahydro-1*H*-isoindole-1,3-dione



C23 H31 N3 O3; Mol wt: 397.5159

ACTION – Uroselective α_{1A} -adrenoceptor antagonist giving a K_i of 0.13 nM at rat submaxillary α_{1A} -adrenoceptors and showing 146-fold selectivity over α_{1B} -adrenoceptors. In functional assays, compound exhibited 47- and 15-fold selectivity, respectively, over α_{1B} - and α_{1D} -adrenoceptors. Its uroselectivity was determined *in vivo* by measuring the effect on mean arterial pressure (MAP) and intraurethral pressure (IUP) following administration to conscious dogs at an oral dose of 10 μ g/kg, resulting in an IUP/MAP AUC ratio of 66. Potentially useful for the treatment of benign prostatic hyperplasia. Other exemplified 1,4-disubstituted piperazine derivatives are:



Compound	R1	Formula
322284	Me	C ₂₂ H ₂₉ N ₃ O ₃
322286	i-Pr	C ₂₄ H ₃₃ N ₃ O ₃
322287	Pr	C ₂₄ H ₃₃ N ₃ O ₃

SOURCE – Ranbaxy.

REFERENCES

1. Anand, N. et al. (Ranbaxy Laboratories Ltd.) 1,4-Disubstd. piperazine derivs. useful as uro-selective α_1 -adrenoceptor blockers. WO 0244151.

TREATMENT OF URINARY
INCONTINENCE

FESOTERODINE

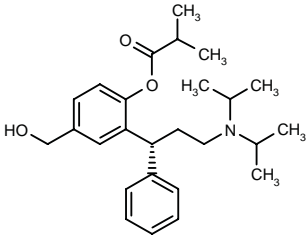
Prop INN

299639

2-Methylpropionic acid 2-[3-(*N,N*-diisopropylamino)-1(*R*)-phenylpropyl]-4-(hydroxymethyl)phenyl ester

Isobutyric acid 2-[3-(diisopropylamino)-1(*R*)-phenylpropyl]-4-(hydroxymethyl)phenyl ester

SPM-907



C26 H37 N O3; Mol wt: 411.5823

ACTION – Antimuscarinic agent, as demonstrated by its ability to antagonize carbachol-induced contractions of rat bladder strips ($pA_2 = 8.7$), with the ability to strongly increase bladder capacity and intercontraction intervals at a dose of 0.01 mg/kg i.v. in a model of urinary incontinence in rats. Results of a phase I study in healthy volunteers demonstrated that ascending multiple oral doses of 4, 8, 12, 20 and 28 mg for 3 days were safe over the whole dose range, and starting from the 12-mg dose, a marked increase in residual urinary volume was observed. A decrease in saliva production and an increase in heart rate were observed at doses of 12 mg and over. Pharmacokinetic analysis showed that compound was rapidly hydrolyzed to the active metabolite SPM-7605, which had linear pharmacokinetics within the dose range of 4-28 mg. Fesoterodine is currently in phase II clinical trials for the treatment of overactive bladder.

SOURCE – Schwarz.

REFERENCES

1. Meese, C. (Schwarz Pharma AG) Stable salts of novel derivs. of 3,3-diphenyl-propylamines. DE 19955190, WO 0135957.

2. Breidenbach, A. et al. Pharmacodynamic profiling of the novel antimuscarinic drug fesoterodine on rat bladder. 32nd Annu Meet Int Continence Soc (Aug 28-31, Heidelberg) 2002, Abst 448.

3. Cawello, W. et al. Multiple dose pharmacokinetics of fesoterodine in human subjects. Naunyn-Schmied Arch Pharmacol 2002, 365(Suppl. 1): Abst 428.

4. Sachse, R. et al. Pharmacodynamics of multiple dose treatment with the novel antimuscarinic drug fesoterodine. Naunyn-Schmied Arch Pharmacol 2002, 365(Suppl. 1): Abst 413.

5. Sachse, R. et al. Safety and pharmacokinetics of the novel antimuscarinic drug fesoterodine in populations of different age or gender. 32nd Annu Meet Int Continence Soc (Aug 28-31, Heidelberg) 2002, Abst 440.

6. *Current development pipeline.* Schwarz Pharma Web Site 2001, Aug 3.

7. *Major development projects.* Schwarz Pharma Web Site 2001, Feb 14.

8. *Proposed international nonproprietary names (Prop. INN): List 84.* WHO Drug Inf 2000, 14(4): 258.

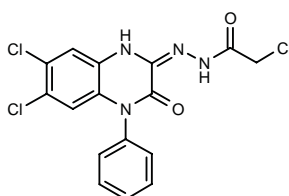
9. *Schwarz updates clinical trial programs.* DailyDrugNews.com (Daily Essentials) 2001, Aug 23.

TREATMENT OF RENAL DISEASES

SJA-7029

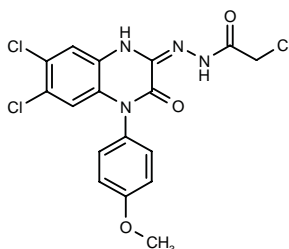
322600

2-Chloro-*N'*-[6,7-dichloro-3-oxo-4-phenyl-3,4-dihydro-quinoxalin-2(1*H*)-ylidene]acetohydrazide



C16 H11 Cl3 N4 O2; Mol wt: 397.6479

ACTION – Potent and selective calpain inhibitor active against both purified μ - and *m*-calpain (IC_{50} = 0.12-0.17 μ M), as well as rabbit renal proximal tubule cell calpain (IC_{50} ~ 30 μ M); less activity was seen against purified cathepsin L (IC_{50} = 4.2 μ M). Compound blocked antimycin A-induced influx of extracellular Ca^{2+} in renal tubule cells, thereby protecting against cell death. The cytoprotective effect of SJA-7029 was confirmed in renal proximal tubule cells subjected to hypoxia/reoxygenation, where the compound improved impaired mitochondrial function and inhibited lactate dehydrogenase (LDH) release as a measure of cell death. Potentially useful for the treatment of acute renal failure. Another related compound is:



SJA-7019 [322599]: C17 H13 Cl3 N4 O3

SOURCE – Senju.

REFERENCES

1. Liu, X. et al. *Cytoprotective properties of novel nonpeptide calpain inhibitors in renal cells.* J Pharmacol Exp Ther 2002, 302(1): 88.

GASTROINTESTINAL DRUGS

AGENTS FOR INFLAMMATORY BOWEL DISEASE

TNX-100

293461

Anti-CD40/CD40L chimeric recombinant human IgG₄ antibody containing the variable domains of the heavy and light chains of the murine MAb 5D12

ch5D12

ACTION – Chimeric recombinant human monoclonal antibody (MAb) that blocks the CD40-CD40L pathway implicated in inflammatory and immune responses. Preclinical studies in marmosets showed that the chimeric MAb was able to prevent the development of experimental autoimmune encephalomyelitis; safety and tolerability studies in cynomolgus monkeys showed that MAb at weekly doses of 5 and 25 mg/kg i.v. was safe and devoid of side effects. Phase I clinical trials in patients with Crohn's disease are in progress.

SOURCES – Chiron; Tanox.

REFERENCES

1. Pasch, M.C. et al. (Tanox, Inc.) *CD40 antagonists for use in treating psoriasis and other inflammatory skin conditions.* WO 0211763.
2. Boon, L. et al. *Preclinical assessment of anti-CD40 Mab 5D12 in cynomolgus monkeys.* Toxicology 2002, 174(1): 53.
3. Boon, L. et al. *Prevention of experimental autoimmune encephalomyelitis in the common marmoset (Callithrix jacchus) using a chimeric antagonist monoclonal antibody against human CD40 is associated with altered B cell responses.* J Immunol 2001, 167(5): 2942.
4. *Grant to study 5D12 in prevention of transplant rejection awarded to Tanox.* DailyDrugNews.com (Daily Essentials) 2000, Sept 8.
5. *Tanox discusses proprietary pipeline at investor conference.* DailyDrugNews.com (Daily Essentials) 2000, Nov 2.
6. *Tanox updates product developments, looks ahead to 2001.* DailyDrugNews.com (Daily Essentials) 2001, Feb 2.

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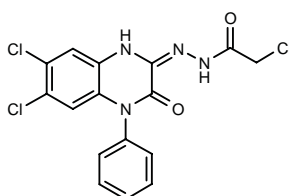
9. *Schwarz updates clinical trial programs.* DailyDrugNews.com (Daily Essentials) 2001, Aug 23.

TREATMENT OF RENAL DISEASES

SJA-7029

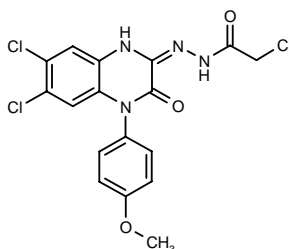
322600

2-Chloro-*N'*-[6,7-dichloro-3-oxo-4-phenyl-3,4-dihydro-quinoxalin-2(1*H*)-ylidene]acetohydrazide



C16 H11 Cl3 N4 O2; Mol wt: 397.6479

ACTION – Potent and selective calpain inhibitor active against both purified μ - and *m*-calpain (IC_{50} = 0.12-0.17 μ M), as well as rabbit renal proximal tubule cell calpain (IC_{50} ~ 30 μ M); less activity was seen against purified cathepsin L (IC_{50} = 4.2 μ M). Compound blocked antimycin A-induced influx of extracellular Ca^{2+} in renal tubule cells, thereby protecting against cell death. The cytoprotective effect of SJA-7029 was confirmed in renal proximal tubule cells subjected to hypoxia/reoxygenation, where the compound improved impaired mitochondrial function and inhibited lactate dehydrogenase (LDH) release as a measure of cell death. Potentially useful for the treatment of acute renal failure. Another related compound is:



SJA-7019 [322599]: C17 H13 Cl3 N4 O3

SOURCE – Senju.

REFERENCES

1. Liu, X. et al. *Cytoprotective properties of novel nonpeptide calpain inhibitors in renal cells.* J Pharmacol Exp Ther 2002, 302(1): 88.

GASTROINTESTINAL DRUGS

AGENTS FOR INFLAMMATORY BOWEL DISEASE

TNX-100

293461

Anti-CD40/CD40L chimeric recombinant human IgG₄ antibody containing the variable domains of the heavy and light chains of the murine MAb 5D12

ch5D12

ACTION – Chimeric recombinant human monoclonal antibody (MAb) that blocks the CD40-CD40L pathway implicated in inflammatory and immune responses. Preclinical studies in marmosets showed that the chimeric MAb was able to prevent the development of experimental autoimmune encephalomyelitis; safety and tolerability studies in cynomolgus monkeys showed that MAb at weekly doses of 5 and 25 mg/kg i.v. was safe and devoid of side effects. Phase I clinical trials in patients with Crohn's disease are in progress.

SOURCES – Chiron; Tanox.

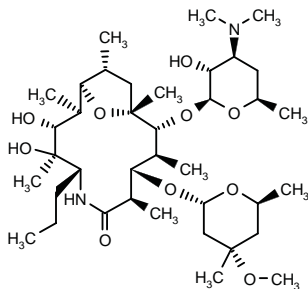
REFERENCES

1. Pasch, M.C. et al. (Tanox, Inc.) *CD40 antagonists for use in treating psoriasis and other inflammatory skin conditions.* WO 0211763.
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6. *Tanox updates product developments, looks ahead to 2001.* DailyDrugNews.com (Daily Essentials) 2001, Feb 2.

TREATMENT OF DISORDERS OF
GASTRIC EMPTYING

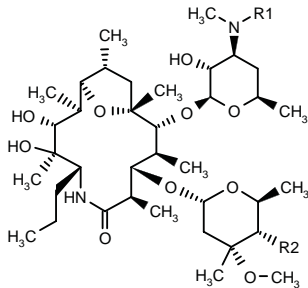
323794

14-Aza-9-deoxo-4'',6-dideoxy-6(*R*),9(*S*)-epoxy-15-methylerythromycin A



C38 H70 N2 O10; Mol wt: 714.9750

ACTION – Macrolide compound with prokinetic activity, expected to be useful for the treatment of gastrointestinal motility disorders. It is reported to possess enhanced activity and a better pharmacokinetic profile compared to previously disclosed motilides. Other exemplified compounds are:



Compound	R1	R2	Formula
323795	H	H	C ₃₇ H ₆₈ N ₂ O ₁₀
323796	i-Pr	H	C ₄₀ H ₇₄ N ₂ O ₁₀
323798	Me	OH	C ₃₈ H ₇₀ N ₂ O ₁₁
323799	H	OH	C ₃₇ H ₆₈ N ₂ O ₁₁
323800	i-Pr	OH	C ₄₀ H ₇₄ N ₂ O ₁₁

SOURCE – Kosan Biosciences.

REFERENCES

1. Santi, D. et al. (Kosan Biosciences, Inc.) *Motilide cpds.* WO 0251855.

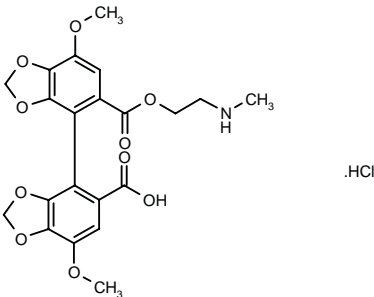
TREATMENT OF LIVER AND BILIARY
TRACT DISORDERS

DDB-S

321836

7,7'-Dimethoxy-4,4'-bi-1,3-benzodioxole-5,5'-dicarboxylic acid 2-(methylamino)ethyl monoester hydrochloride

Lebecel



C21 H21 N O10 . HCl; Mol wt: 483.8548

ACTION – Hepatoprotectant able to protect rat hepatocytes from toxicity induced by CCl₄ *in vitro* and proven active against CCl₄-induced hepatic toxicity in rats. A dose of 50 mg/kg i.p. significantly attenuated the CCl₄-induced increase in serum alanine transaminase, aspartate transaminase and alkaline phosphatase. In healthy volunteers, compound (7.5, 15, 30 and 60 mg by 60-min i.v. infusion) was safe and well tolerated and exhibited linear pharmacokinetics. It is presently in phase II clinical studies in patients with acute or chronic hepatitis.

SOURCES – Daewoo Pharmaceuticals; Pusan National University, Pusan (KR).

REFERENCES

1. Lee, C.-H. *Soluble DDB derivs. and preparation method thereof.* KR 231013.

2. Choi, W.C. et al. *Influence of temperature and pH on the stability of dimethoxy biphenyl monocarboxylate HCl solutions.* Arch Pharmacol Res 2001, 24(2): 159.

3. Chung, J. et al. *Evaluation of safety, tolerability, and pharmacokinetics of DDB-S(injection): A phase I clinical trial.* Clin Pharmacol Ther 2002, 71(2): Abst WP111-21.

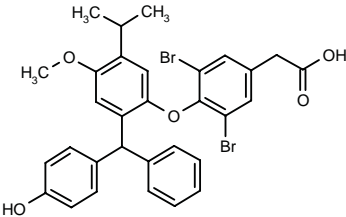
4. Sy, O. et al. *Pharmacokinetics and hepatoprotective effects of 2-methylaminoethyl-4,4'-dimethoxy-5,6,5'-dimethylenedioxybiphenyl-2-carboxylic acid-2'-carboxylate monohydrochloride in rats with CCl4-induced acute hepatic failure.* J Pharm Pharmacol 2000, 52(9): 1099.

ENDOCRINE DRUGS

ANTIDIABETIC DRUGS

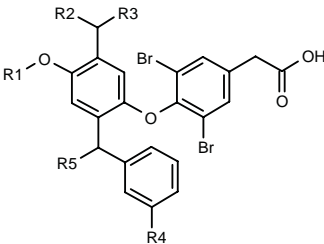
322296

2-[3,5-Dibromo-4-[2-[1-(4-hydroxyphenyl)-1-phenyl-methyl]-5-isopropyl-4-methoxyphenoxy]phenyl]acetic acid



C31 H28 Br2 O5; Mol wt: 640.3652

ACTION – Liver-selective glucocorticoid receptor antagonist expected to be useful for the treatment of type 1 and type 2 diabetes, Cushing’s syndrome and inflammation, among other disorders associated with glucocorticoid metabolism. Other exemplified compounds are:



Compound	R1	R2	R3	R4	R5	Formula
322297	Me	Me	Me	H	2-OH-5-Cl-Ph	C ₃₁ H ₂₇ Br ₂ ClO ₅
322298	Me	Me	Me	H	3-indolyl	C ₃₃ H ₂₉ Br ₂ NO ₄
322299	Me	Me	Me	Me	2-OH-5-Br-Ph	C ₃₂ H ₂₉ Br ₃ O ₅
322300	Me	Me	Me	Me	2-OH-3,6-(Me)2-Ph	C ₃₄ H ₃₄ Br ₂ O ₅
322301	Me	Me	Me	Me	2-OH-5-(CO ₂ MeCH ₂ CH ₂)-Ph	C ₃₆ H ₃₆ Br ₂ O ₇
322302	Me	Me	Me	Me	2,3,4-(MeO)3-6-OH-Ph	C ₃₅ H ₃₆ Br ₂ O ₈
322303	Me	-(CH ₂) ₄ -	Me	Me	2-OH-3-MeO-5-Me-Ph	C ₃₆ H ₃₆ Br ₂ O ₆
322304	H	Me	Me	Me	2,5-(OH)2-Ph	C ₃₁ H ₂₈ Br ₂ O ₆

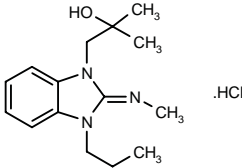
SOURCE – Karo Bio.

REFERENCES

1. Gillner, M. et al. (Karo Bio AB) *Cpds. active at the glucocorticoid receptor III*. WO 0244120.

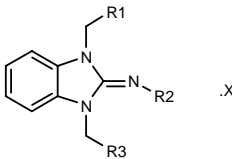
322401

2-Methyl-1-[2-(methylimino)-3-propyl-2,3-dihydro-1*H*-benzimidazol-1-yl]propan-2-ol hydrochloride



C15 H23 N3 O . HCl; Mol wt: 297.8276

ACTION – Insulin secretagogue for use in the treatment of diabetes. Compound is reported to have a beneficial effect in high blood glucose states, while causing no severe side effects such as hypoglycemia. In murine pancreatic β-cells, it increased insulin secretion by 246% at 10 μM in the presence of high glucose concentrations (11.2 mM), whereas it displayed no activity at sulfonylurea receptors at concentrations up to 1 mM. Other exemplified imidazole compounds are:



Compound	R1	R2	R3	X	Formula
322402	4-Cl-PhOC(Me)2CO	Me	Et	HBr	C ₂₂ H ₂₆ ClN ₃ O ₂ ..HBr
322403	CH(t-Bu)2	Me	Et	HCl	C ₂₁ H ₃₅ N ₃ .HCl
322404	t-BuCO	H	Et	HBr	C ₁₆ H ₂₃ N ₃ O..HBr
322405	COC(Et)2Me	H	Et	HBr	C ₁₈ H ₂₇ N ₃ O..HBr
322406	cyclohexyl-CH(OH)	H	Et	HCl	C ₁₈ H ₂₇ N ₃ O.HCl
322407	CH(OH)C(Me)2CH2Cl	H	Et	HCl	C ₁₅ H ₂₂ ClN ₃ O.HCl
322408	CH(OH)C(Me)2Et	H	C(Me)2-CH2OH	HCl	C ₁₉ H ₃₁ N ₃ O ₂ .HCl

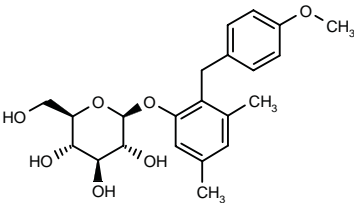
SOURCE – Japan Tobacco.

REFERENCES

1. Goto, H. et al. (Japan Tobacco Inc.) *Imidazole cpds. and their use*. JP 2002155060.

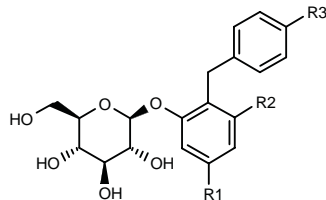
322575

2-(4-Methoxybenzyl)-3,5-dimethylphenyl β-D-glucopyranoside



C22 H28 O7; Mol wt: 404.4562

ACTION – Inhibitor of the sodium-dependent glucose transporter SGLT2 proven to inhibit the uptake of methyl α -D-glucopyranoside by SGLT2-transfected COS-7 cells with an IC₅₀ of 290 nM. *In vivo*, compound (i.v.) dose-dependently increased urinary glucose excretion in rats. In acute toxicity tests, no deaths were observed in mice at a dose of 300 mg/kg s.c. Potentially useful for the treatment of diabetes, complications related therewith and obesity. Other exemplified glucopyranosyloxybenzyl benzene derivatives are:



Compound	R1	R2	R3	Formula
322576	H	H	CH=CHCH2OH	C ₂₂ H ₂₆ O ₇
322577	NH2	H	Et	C ₂₁ H ₂₇ NO ₆
322578	Me	Me	(CH2)3OH	C ₂₄ H ₃₂ O ₇
322579	Me	Me	CH2CH2OH	C ₂₃ H ₃₀ O ₇

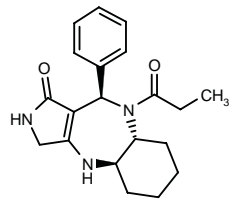
SOURCE – Kissei.

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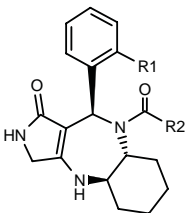
322626

(4*R*,8*aR*,10*R*)-10-Phenyl-9-propionyl-1,2,3,4,4*a*,5,6,7,8,8*a*,9,10-dodecahydropyrrolo[3,4-*b*][1,5]benzodiazepin-1-one



C20 H25 N3 O2; Mol wt: 339.4365

ACTION – Agent with the ability to stimulate glucose transport, and thus potentially useful for the treatment of diabetes, diabetic peripheral neuropathy, diabetic restenosis, glucose tolerance failure and obesity. It potentiated glucose transport in rat testis preparations with an EC₅₀ of 1.5 μ g/ml. *In vivo*, compound demonstrated a glucose-lowering effect following oral administration to mice at a dose of 100 mg/kg. Other exemplified lactam compounds include the following:



Compound	R1	R2	Formula
322627	OMe	OMe	C ₂₀ H ₂₆ N ₃ O ₄
322628	OEt	Et	C ₂₂ H ₂₈ N ₃ O ₃
322629	Me	CH2OEt	C ₂₂ H ₂₉ N ₃ O ₃
322630	Et	CH2OEt	C ₂₃ H ₃₁ N ₃ O ₃
322631	Et	Me	C ₂₁ H ₂₇ N ₃ O ₂
322632	Br	CH2OEt	C ₂₁ H ₂₆ BrN ₃ O ₃
322633	Cl	Me	C ₁₉ H ₂₂ ClN ₃ O ₂
322634	H	CH2OEt	C ₂₁ H ₂₇ N ₃ O ₃
322635	H	OMe	C ₁₉ H ₂₃ N ₃ O ₃

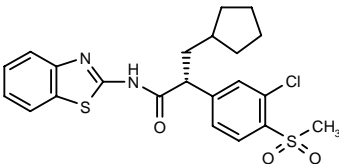
SOURCE – Ajinomoto.

REFERENCES

1. Iino, Y. et al. (Ajinomoto Co., Inc.) *Lactam cpds. and medicinal use thereof*. WO 0244180.

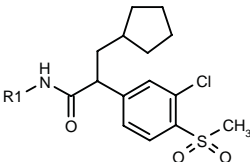
322741

N-(2-Benzothiazolyl)-2(*R*)-[3-chloro-4-(methylsulfonyl)-phenyl]-3-cyclopentylpropionamide



C22 H23 Cl N2 O3 S2; Mol wt: 463.0197

ACTION – Glucokinase activator that stimulates insulin secretion and demonstrated *in vivo* blood glucose-lowering activity following oral administration to mice at a dose of 50 mg/kg. Potentially useful for the treatment of type 2 diabetes. Other exemplified fused heteroaromatic compounds are:



Compound	R1	Formula
322742	2-benzimidazolyl	C ₂₂ H ₂₄ ClN ₃ O ₃ S
322743	2-quinolyl	C ₂₄ H ₂₅ ClN ₂ O ₃ S

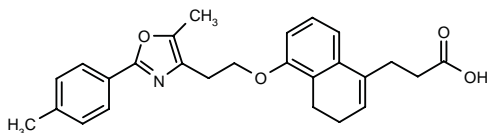
SOURCE – Roche.

REFERENCES

1. Corbett, W.L. et al. (F. Hoffmann-La Roche AG) *Fused heteroaromatic glucokinase activators*. WO 0246173.

323843

3-[5-[2-[5-Methyl-2-(4-methylphenyl)oxazol-4-yl]ethoxy]-3,4-dihydronaphthalen-1-yl]propionic acid



C26 H27 N O4; Mol wt: 417.5023

ACTION – A representative compound from a series of dihydronaphthalene derivatives with peroxisome proliferator-activated receptor (PPAR)-modulating activity. Compound demonstrated PPAR α and PPAR γ receptor-agonist activity *in vitro* and is potentially useful as a hypoglycemic and hypolipidemic agent.

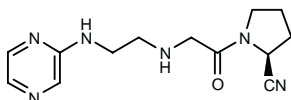
SOURCE – Ono.

REFERENCES

1. Tajima, H. et al. (Ono Pharmaceutical Co., Ltd.) *Dihydronaphthalene deriv. cpds. and drugs containing these cpds. as the active ingredient*. WO 0251820.

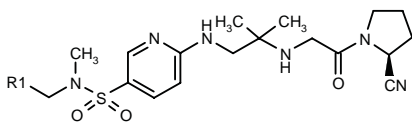
323992

1-[2-[2-(Pyrazin-2-ylamino)ethylamino]acetyl]pyrrolidine-2(S)-carbonitrile

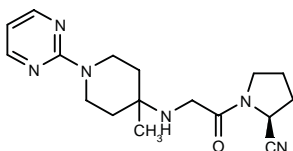


C13 H21 N5 O; Mol wt: 263.3429

ACTION – Dipeptidyl-peptidase IV (DPP-IV) inhibitor (IC₅₀ = 31 nM), potentially useful for the treatment or prevention of type 2 diabetes and complications associated therewith. Other exemplified compounds are:



Compound	R1	Formula
323993	H	C ₁₈ H ₃₁ N ₅ O ₃ S
323994	Me	C ₁₉ H ₃₃ N ₅ O ₃ S



323995: C17 H27 N5 O

SOURCE – Kyowa Hakko.

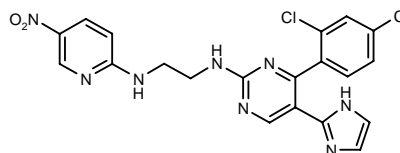
REFERENCES

1. Matsuno, K. et al. (Kyowa Hakko Kogyo Co., Ltd.) *Dipeptidyl peptidase IV inhibitor*. WO 0251836.

CHIR-98023^{1-3,5-7}**305195**

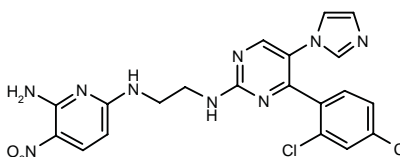
N¹-[4-(2,4-Dichlorophenyl)-5-(1*H*-imidazol-2-yl)pyrimidin-2-yl]-N²-(5-nitropyridin-2-yl)ethane-1,2-diamine

CT-98023



C20 H16 Cl2 N8 O2; Mol wt: 471.3064

ACTION – Selective glycogen synthase kinase-3 (GSK-3) inhibitor able to produce concentration-dependent activation of glycogen synthase in human skeletal muscle cells, with maximal effects at 1-2 μ M following acute (30 min) treatment; in this assay, insulin itself or LiCl was less potent. After chronic (4 days) treatment, compound showed a sustained activation of basal and insulin-stimulated glucose uptake, a decrease in GSK-3 protein and GSK-3 total activity, and an increase in insulin receptor substrate IRS-1 protein. After cotreatment of muscle cells with submaximal concentrations of compound and insulin, an additive effect was seen on glycogen synthase activation. Potentially useful for controlling glucose metabolism and insulin action in skeletal muscle cells of type 2 diabetes patients. Another related compound is:



CHIR-98014 [319088]:*,1,2,4,6,7 C20 H17 Cl2 N9 O2
CT-98014

SOURCE – Chiron.

REFERENCES

1. Nuss, J.M. et al. (Chiron Corp.) *Inhibitors of glycogen synthase kinase 3*. EP 1087963, US 6417185, WO 9965897.

2. Nuss, J.M. et al. (Chiron Corp.) *Inhibitors of glycogen synthase kinase 3*. WO 0220495.

3. Cline, G.W. et al. *Effects of a novel glycogen synthase kinase-3 (GSK-3) inhibitor on liver and muscle glycogen synthesis in awake ZDF (fa/fa) diabetic rats*. Diabetes 2001, 50(Suppl. 2): Abst 1350-P.

4. Henriksen, E.J. et al. *In vitro glycogen synthase kinase-3 inhibition enhances insulin-stimulated glucose transport in skeletal muscle of the Zucker diabetic fatty rat*. Diabetes 2000, 49(Suppl. 1): Abst 63-OR.

5. Henriksen, E.J. et al. *Oral treatment with a glycogen synthase kinase-3 inhibitor improves glucose tolerance and skeletal muscle glucose transport activity in Zucker diabetic fatty rats*. 37th Annu Meet Eur Assoc Study Diabetes (Sept 9-13, Glasgow) 2001, Abst 681.

6. Nikoulina, S.E. et al. *Inhibition of glycogen synthase kinase 3 improves insulin action and glucose metabolism in human skeletal muscle*. Diabetes 2002, 51(7): 2190.

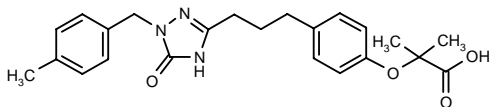
7. Samuels, I. et al. *Efficacy and pharmacological properties of novel glycogen synthase kinase 3 (GSK-3) inhibitors in rodent models of type 2 diabetes*. Diabetes 2001, 50(Suppl. 2): Abst 1352-P.

*Identified compound **319088** (see **319083**) Drug Data Rep 2002, 024(06): 0505.

LY-518674

323845

2-Methyl-2-[4-[3-[1-(4-methylbenzyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl]propyl]phenoxy]propionic acid



C23 H27 N3 O4; Mol wt: 409.4833

ACTION – Potent and selective peroxisome proliferator-activated receptor PPAR α agonist with nanomolar affinity for the receptor. Selected as a candidate for clinical studies in diabetic patients.

SOURCE – Lilly.

REFERENCES

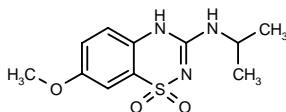
1. Mantlo, N.B. et al. (Eli Lilly and Company) *Peroxisome proliferator activated receptor α agonists*. WO 0238553.
2. Braden, T. et al. *Novel acid-catalyzed synthesis of triazolones from acyl semicarbazides*. 224th ACS Natl Meet (Aug 18-22, Boston) 2002, Abst MEDI 381.
3. Wang, X. et al. *Synthesis and SAR studies toward a selective PPAR α -agonist*. 224th ACS Natl Meet (Aug 18-22, Boston) 2002, Abst MEDI 363.

NNC-55-9216

321838

3-(Isopropylamine)-7-methoxy-4H-1,2,4-benzothiadiazine 1,1-dioxide

BPDZ-216



C11 H15 N3 O3 S; Mol wt: 269.3235

ACTION – Potent and selective β -cell ATP-sensitive potassium (K_{ATP}) channel (SUR1/Kir6.2) opener (EC_{50} = 16 μ M) inactive against other K_{ATP} channels including cardiac Kir6.2/SUR2A and smooth muscle Kir6.2/SUR2B channels. The compound appeared to interact with a different region of SUR than other potassium channel openers, i.e., pinacidil and cromakalim. A useful lead for the development of β -cell-selective potassium channel openers devoid of the side effects of diazoxide and useful for the treatment of hyperinsulinemic states.

SOURCE – Novo Nordisk.

REFERENCES

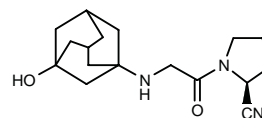
1. Pirotte, B. et al. (Novo Nordisk A/S) *1,2,4-Benzothiadiazine derivs. their preparation and use*. EP 0906297, JP 2000512641, US 6242443, WO 9749692.
2. Dabrowski, M. et al. *A novel SUR1/Kir6.2 specific K_{ATP} channel opener*. J Physiol 2001, 533P115P.
3. Dabrowski, M. et al. *The novel diazoxide analog 3-isopropylamino-7-methoxy-4H-1,2,4-benzothiadiazine 1,1-dioxide is a selective Kir6.2/SUR1 channel opener*. Diabetes 2002, 51(6): 1896.

NVP-LAF-237*

291074

1-[2-(3-Hydroxyadamant-1-ylamino)acetyl]pyrrolidine-2(S)-carbonitrile

LAF-237



C17 H25 N3 O2; Mol wt: 303.4035

ACTION – Potent and highly selective dipeptidyl-peptidase IV (DPP-IV) inhibitor with IC_{50} values of 2.7 and 2.1 nM against human and rat enzyme, respectively, and > 75,000 fold selectivity over DPP-II, prolyl endopeptidase, trypsin and aminopeptidase P. Following oral administration to Zucker fatty rats, compound rapidly inhibited plasma DPP-IV activity (90% inhibition at 30 min after 1 μ mol/kg) and increased plasma intact GLP-1 levels after oral glucose challenge, resulting in increased glucose-dependent insulin secretion and improved glucose homeostasis. When compound was given in combination with the insulin sensitizer pioglitazone during an oral glucose tolerance tests in obese Zucker rats, a synergistic effect on glucose-lowering was observed. Potentially useful for the treatment of type 2 diabetes.

SOURCE – Novartis.

REFERENCES

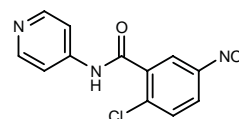
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2. Villhauer, E.B. (Novartis AG) *N-Substd. 2-cyanopyrrolidines*. EP 1137635, US 6166063, WO 0034241.
3. Burkey, B.F. et al. *Combination treatment of a DPP-IV inhibitor NVP-LAF237 with pioglitazone completely normalized glucose tolerance in adult obese Zucker rats*. Diabetes 2002, 51(Suppl. 2): Abst 1383-P.
4. Hughes, T.E. et al. *NVP-LAF237, a highly selective and long-acting dipeptidyl peptidase IV inhibitor*. Diabetes 2002, 51(Suppl. 2): Abst 272-OR.
5. Reinhardt, J. *Innovation and productivity drive sustained growth*. Novartis R&D Invest Semin (Dec 6, Basel) 2000.
6. *Novartis - Accelerating growth*. 22nd Goldman Sachs Health Care Conf (June 11-14, Laguna Niguel) 2001.
7. *Novartis R&D day 2001: Solid platform for sustained growth*. DailyDrugNews.com (Daily Essentials) 2001, Nov 7.

*Identified compound **291074** Drug Data Rep 2000, 022(10): 0905.

T-0070907

323259

2-Chloro-5-nitro-N-(4-pyridyl)benzamide



C12 H8 Cl N3 O3; Mol wt: 277.6662

ACTION – High-affinity peroxisome proliferator-activated receptor PPAR γ ligand ($K_i = 1$ nM) with > 800-fold selectivity over PPAR α and PPAR δ receptors and *in vitro* functional antagonist activity in both a cell-based reporter gene assay and an adipocyte differentiation assay. Potentially useful for the treatment of diabetes.

SOURCES – Sankyo; Tularik.

REFERENCES

1. Amemiya, Y. et al. (Sankyo Co., Ltd.) *PPAR γ modulators*. WO 0183427.
2. Lee, G. et al. T0070907, a selective ligand for peroxisome proliferator-activated receptor γ , functions as an antagonist of biochemical and cellular activities. J Biol Chem 2002, 277(22): 19649.

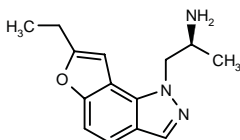
TREATMENT OF MALE SEXUAL DYSFUNCTION

YM-348*

312930

1-(7-Ethyl-1*H*-furo[2,3-*g*]indazol-1-yl)propan-2(*S*)-amine

2-(7-Ethyl-1*H*-furo[2,3-*g*]indazol-1-yl)-1(*S*)-methylethylamine



C₁₄ H₁₇ N₃ O; Mol wt: 243.3083

ACTION – Potent 5-HT_{2C} receptor agonist with high affinity and selectivity for human 5-HT_{2C} receptors over 5-HT_{2A} receptors ($K_i = 0.89$ and 13 nM, respectively) and an EC₅₀ value of 1.0 nM in an *in vitro* functional assay of phosphoinositol hydrolysis in CHO cells expressing human 5-HT_{2C} receptors. In addition, compound had good activity in a rat model of penile erection following either oral (MED = 0.3 mg/kg) or s.c. administration (MED = 0.03 mg/kg). Potentially useful for the treatment of erectile dysfunction.

SOURCE – Yamanouchi.

REFERENCES

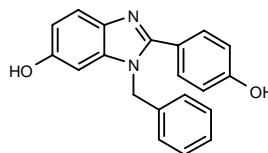
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*Identified compound **312930** Drug Data Rep 2002, 024(02): 0145.

TREATMENT OF GYNECOLOGICAL DISORDERS

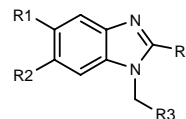
322714

1-Benzyl-2-(4-hydroxyphenyl)-1*H*-benzimidazol-6-ol



C₂₀ H₁₆ N₂ O₂; Mol wt: 316.3584

ACTION – Selective estrogen receptor ER β ligand reportedly useful for the treatment of Alzheimer's disease, anxiety, depression, osteoporosis, cardiovascular disease, rheumatoid arthritis and prostate cancer. Other exemplified benzimidazole compounds include the following:



Compound	R1	R2	R3	R4	Formula
322715	H	OH	Pr	4-OH-Ph	C ₁₇ H ₁₈ N ₂ O ₂
322716	H	OH	4-F-Ph	4-OH-Ph	C ₂₀ H ₁₅ FN ₂ O ₂
322717	H	OH	3-Cl-PhCH ₂	4-OH-Ph	C ₂₁ H ₁₇ ClN ₂ O ₂
322718	H	OH	4-Et-PhCH ₂	2-Cl-4-OH-Ph	C ₂₃ H ₂₁ ClN ₂ O ₂
322719	H	OH	CH ₂ CH ₂ Ph	4-OH-Ph	C ₂₂ H ₂₀ N ₂ O ₂
322720	OH	H	H	4-OH-Ph	C ₁₄ H ₁₂ N ₂ O ₂
322721	H	OH	2-thienyl-CH ₂	4-imidazolyl	C ₁₆ H ₁₄ N ₄ OS
322722	H	OH	2-thienyl-CH ₂	4-(MeSO ₂)-Ph	C ₂₀ H ₁₈ N ₂ O ₃ S ₂
322723	H	OH	2-thienyl-CH ₂	4-MeO-Ph	C ₂₀ H ₁₈ N ₂ O ₂ S

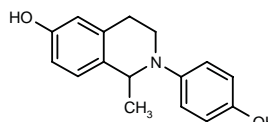
SOURCE – AstraZeneca.

REFERENCES

1. Barlaam, B. et al. (AstraZeneca AB) *Therapeutic benzimidazole cpds*. WO 0246168.

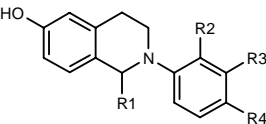
322724

2-(4-Hydroxyphenyl)-1-methyl-1,2,3,4-tetrahydroisoquinolin-6-ol



C₁₆ H₁₇ N O₂; Mol wt: 255.3153

ACTION – Selective estrogen receptor ER β ligand (EC₅₀ = 143 nM) with 7-fold selectivity over ER α receptors. Potentially useful for the treatment of Alzheimer's disease, anxiety, depression, osteoporosis, cardiovascular disease, rheumatoid arthritis and prostate cancer. Other exemplified compounds are:



Compound	R1	R2	R3	R4	Formula
322725	H	Me	H	OH	C ₁₆ H ₁₇ NO ₂
322726	H	NO2	H	OH	C ₁₅ H ₁₄ N ₂ O ₄
322727	3-furyl	H	OH	Me	C ₂₀ H ₁₉ NO ₃

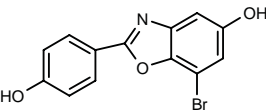
SOURCE – AstraZeneca.

REFERENCES

1. Barlaam, B. and Dantzman, C. (AstraZeneca AB) *Therapeutic cpds.* WO 0246164.

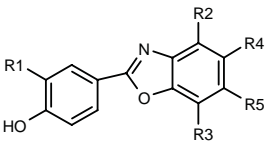
323683

7-Bromo-2-(4-hydroxyphenyl)benzoxazol-5-ol



C13 H8 Br N O3; Mol wt: 306.1142

ACTION – Modulator of estrogen ERβ receptors with K_i values of 0.38 and 5.6 nM, respectively, at ERβ and ERα receptors in binding assays. In functional cell-based assays, compound demonstrated ERβ-agonist activity (EC₅₀ = 0.017 nM) and 363-fold selectivity over ERα receptors. Potentially useful in estrogen replacement therapy, and particularly in the treatment of Alzheimer's disease, anxiety and depressive disorders, osteoporosis, cardiovascular disease, rheumatoid arthritis and prostate cancer. Other exemplified compounds are:



Compound	R1	R2	R3	R4	R5	Formula
323684	H	Cl	H	H	OH	C ₁₃ H ₈ ClNO ₃
323685	H	Me	H	H	OH	C ₁₄ H ₁₁ NO ₃
323686	H	OH	H	H	OH	C ₁₃ H ₉ NO ₄
323687	H	H	H	OH	H	C ₁₃ H ₉ NO ₃
323688	H	H	H	OMe	H	C ₁₄ H ₁₁ NO ₃
323689	Cl	H	Br	OH	H	C ₁₃ H ₇ BrClNO ₃
323690	H	H	CN	OH	H	C ₁₄ H ₈ N ₂ O ₃
323691	H	H	CONH2	OH	H	C ₁₄ H ₁₀ N ₂ O ₄

SOURCE – AstraZeneca.

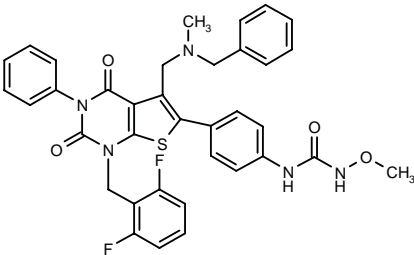
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TAK-013*

295240

N-[4-[5-(N-Benzyl-N-methylaminomethyl)-1-(2,6-difluoro-benzyl)-2,4-dioxo-3-phenyl-1,2,3,4-tetrahydrothieno-[2,3-d]pyrimidin-6-yl]phenyl]-N'-methoxyurea



C36 H31 F2 N5 O4 S; Mol wt: 667.7339

ACTION – Potent, orally active, nonpeptide gonadotropin-releasing hormone (GnRH) receptor antagonist with high affinity for (IC₅₀ = 0.1 nM) and potent *in vitro* functional antagonism at the human GnRH receptor (EC₅₀ = 0.06 nM). In castrated cynomolgus monkeys, oral administration at a dose of 10 mg/kg produced potent and long-lasting (> 24 h) suppression of plasma luteinizing hormone (LH) levels. Early clinical studies in healthy male volunteers showed that compound given as a single oral dose (10-200 mg) dose-dependently suppressed serum LH and testosterone levels. Further clinical trials are under way to confirm its potential therapeutic use in the treatment of sex hormone-dependent disorders including endometriosis and uterine fibrosis.

SOURCE – Takeda.

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2. Furuya, S. and Suzuki, N. (Takeda Chemical Industries, Ltd.) *Preventives/remedies for Alzheimer's disease.* WO 0178780.

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7. Suzuki, H. and Hata, Y. (Takeda Chemical Industries, Ltd.) *Medicinal compsns. of nonpeptidyl gonadotropin-releasing hormone agonist or antagonist, process for producing the same and use thereof.* WO 0247722.

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9. Sasaki, S. et al. *Discovery of the thieno[2,3-d]pyrimidine-2,4-dione derivative TAK-013: Highly potent and orally active nonpeptide LHRH (GnRH) antagonist (II).* 224th ACS Natl Meet (Aug 18-22, Boston) 2002, Abst MEDI 354.

10. Suzuki, N. et al. *TAK-013: A novel, potent, and orally active nonpeptide antagonist for the human gonadotropin-releasing hormone receptor.* 84th Annu Meet Endocr Soc (June 19-22, San Francisco) 2002, Abst OR7-2.

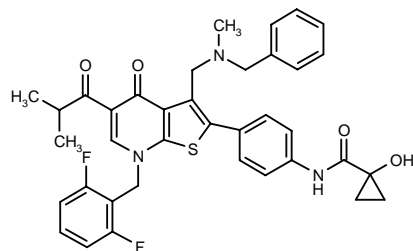
11. *Product pipeline.* Takeda Chemical Industries Web Site 2001, Nov 6.

*Identified compound **295240** Drug Data Rep 2001, 023(02): 0182.

TAK-810

324010

N-[4-[3-(N-Benzyl-N-methylaminomethyl)-7-(2,6-difluorobenzyl)-5-isobutyryl-4-oxo-4,7-dihydrothieno[2,3-b]pyridin-2-yl]phenyl]-1-hydroxycyclopropanecarboxamide



C37 H35 F2 N3 O4 S; Mol wt: 655.7625

ACTION – Potent and orally active nonpeptide gonadotropin-releasing hormone (GnRH) receptor antagonist that exhibited high affinity ($IC_{50} = 0.1$ nM) and potent *in vitro* functional antagonism at the human GnRH receptor ($EC_{50} = 0.11$ nM). Oral doses of 10 and 30 mg/kg produced high and long-lasting (> 24 h) suppression of plasma luteinizing hormone (LH) levels in castrated cynomolgus monkeys. Compound is in early-stage clinical trials for the treatment of sex hormone-dependent disorders including endometriosis and uterine fibrosis.

SOURCE – Takeda.

REFERENCES

1. Furuya, S. and Suzuki, N. (Takeda Chemical Industries, Ltd.) *Preventives/remedies for Alzheimer's disease*. WO 0178780.

2. Furuya, S. et al. (Takeda Chemical Industries, Ltd.) *Thienopyridine cpds., their production and use*. EP 1090010, JP 2000219690, JP 2000219691, US 6262267, US 6329388, WO 0000493.

3. Igari, Y. and Kamei, S. (Takeda Chemical Industries, Ltd.) *Medicinal preparations for treating sex hormone-dependent diseases*. WO 0202144.

4. Nakano, Y. et al. (Takeda Chemical Industries, Ltd.) *Solid preparations*. WO 0224230.

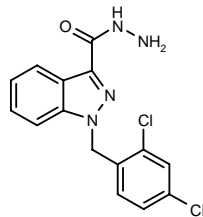
5. Imada, T. et al. *Discovery of the thieno[2,3-b]pyridin-4-one derivative TAK-810: Highly potent and orally active nonpeptide LHRH (GnRH) antagonist (I)*. 224th ACS Natl Meet (Aug 18-22, Boston) 2002, Abst MEDI 353.

CONTRACEPTIVES

AF-2364

322728

1-(2,4-Dichlorobenzyl)-1H-indazole-3-carbohydrazide



C15 H12 Cl2 N4 O; Mol wt: 335.1928

ACTION – Male contraceptive, an antispermato-genic compound proven to deplete germ cells from the epithelium by an unknown mechanism. The compound blocked cAMP-activated chloride currents in rat epididymal cells ($IC_{50} = 170.6$ μ M) and chloride secretion in the epididymis, suggesting that it may alter fluid content in the intraluminal compartment. It did not alter levels of follicle-stimulating hormone (FSH) and causes only minimal changes in luteinizing hormone (LH) and testosterone. It is orally bioavailable and preliminary toxicity studies in mice showed no liver or kidney toxicity.

SOURCE – Angelini.

REFERENCES

1. Silvestrini, B. and Cheng, C.Y. (Angelini Pharmaceuticals Inc.) *3-Substd. 1-benzyl-1H-indazole derivs. as antifertility agents*. US 6001865.

2. Cheng, C.Y. et al. *Indazole carboxylic acids in male contraception*. Contraception 2002, 65(4): 265.

3. Cheng, C.Y. et al. *Two new male contraceptives exert their effects by depleting germ cells prematurely from the testis*. Biol Reprod 2001, 65(2): 449.

4. Grima, J. et al. *Reversible inhibition of spermatogenesis in rats using a new male contraceptive, 1-(2,4-dichlorobenzyl)-indazole-3-carbohydrazide*. Biol Reprod 2001, 64(5): 1500.

ETONOGESTREL/ETHINYLESTRADIOL

New combination

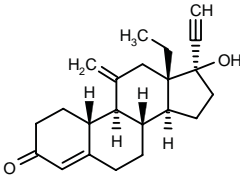
294942

Combined contraceptive vaginal ring made of Silastic containing etonogestrel and ethinylestradiol

ETONOGESTREL

090420

(17 α)-13-Ethyl-17-hydroxy-11-methylene-18,19-dinor-pregn-4-en-20-yn-3-one

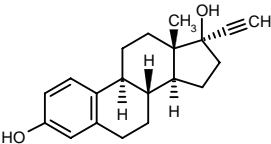


C22 H28 O2 ; Mol wt: 324.4612

ETHINYLESTRADIOL

125559

19-Nor-17 α -pregna-1,3,5(10)-trien-20-yne-3,17-diol



C20 H24 O2 ; Mol wt: 296.4130

ACTION – Combination of two hormonal contraceptives, the progestin etonogestrel and the estrogen ethinylestradiol, that acts by suppressing gonadotropins, inhibiting ovulation and producing changes in the cervical mucus and endometrium.

INDICATION – Female contraception.

PRESENTATION – Vaginal ring releasing 15 µg/day ethinylestradiol and 120 µg/day etonorgestrel over 3 weeks.

PROPRIETARY NAME – NuvaRing (US).

SOURCE – Organon.

REFERENCES

1. Mulders, T.M. and Dieben, T.O. *Use of the novel combined contraceptive vaginal ring NuvaRing for ovulation inhibition.* Fertil Steril 2001, 75(5): 865.

2. Roumen, F.J. et al. *Efficacy, tolerability and acceptability of a novel contraceptive vaginal ring releasing etonogestrel and ethinyl oestradiol.* Hum Reprod 2001, 16(3): 469.

3. Roumen, F.J. et al. *The cervico-vaginal epithelium during 20 cycles' use of a combined contraceptive vaginal ring.* Hum Reprod 1996, 11(11): 2443.

4. Timmer, C.J. and Mulders, T.M. *Pharmacokinetics of etonogestrel and ethinylestradiol released from a combined contraceptive vaginal ring.* Clin Pharmacokin 2000, 39(3): 233.

5. *First monthly vaginal contraceptive ring granted marketing approval in the U.S.* DailyDrugNews.com (Daily Essentials) 2001, Oct 5.

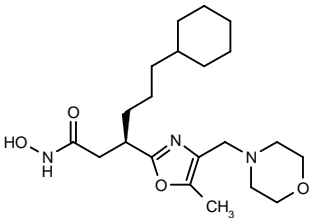
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DERMATOLOGIC DRUGS

WOUND-HEALING AGENTS

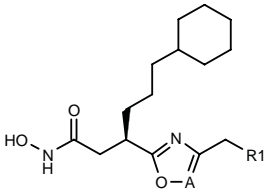
323352

6-Cyclohexyl-3(R)-[5-methyl-4-(morpholin-4-ylmethyl)-oxazol-2-yl]hexanohydroxamic acid



C21 H35 N3 O4; Mol wt: 393.5245

ACTION – Procollagen C-proteinase (PCP) inhibitor; IC₅₀ = 37 nM against enzyme expressed in CHO cells) with selectivity over matrix metalloproteinases MMP-1 (interstitial collagenase), MMP-2 (gelatinase A), MMP-9 (gelatinase B) and/or MMP-14 (MT-1 MMP). Potentially useful for the antiscarring treatment of wounds. Other exemplified hydroxamic acid derivatives are:



Compound	R1	A	Formula
323353	2-Pyr-SO2NH	N	C ₂₀ H ₂₉ N ₅ O ₅ S
323354	t-BuNHSO2NH	N	C ₁₈ H ₃₅ N ₅ O ₅ S
323355	NH2	N	C ₁₅ H ₂₆ N ₄ O ₃
323356	cyclopentyl-NH	N	C ₂₀ H ₃₄ N ₄ O ₃
323357	4-THP-NH	N	C ₂₀ H ₃₄ N ₄ O ₄
323358	N(Me)CH2CONHMe	N	C ₁₉ H ₃₃ N ₅ O ₄
323359	4-morpholinyl	CH	C ₂₀ H ₃₃ N ₅ O ₄

SOURCE – Pfizer.

REFERENCES

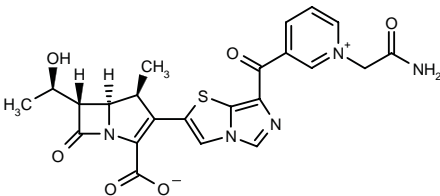
1. Datta, U. et al. (Pfizer Ltd.;Pfizer Inc.) *3-Ox(adi)azolylpropanohydroxamic acids useful as procollagen C-proteinase inhibitors.* WO 0250046.

ANTIINFECTIVE THERAPY

ANTIBIOTICS

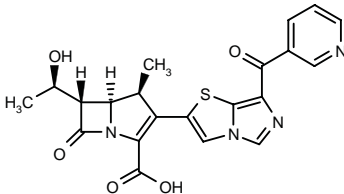
322446

(1R,5S,6S)-[2-[7-[1-(Carbamoylmethyl)pyridin-1-ium-3-ylcarbonyl]imidazo[5,1-b]thiazol-2-yl]-6-[1(R)-hydroxyethyl]-1-methyl-1-carba-2-penem-3-carboxylate



C23 H21 N5 O6 S; Mol wt: 495.5139

ACTION – Carbapenem antibiotic with MIC values of < 0.1 µg/ml against a panel of bacterial strains. *In vivo*, it gave an ED₅₀ value of 0.07 mg/animal s.c. in mice with infections caused by methicillin-resistant *Staphylococcus aureus*. In acute toxicity tests, it caused no deaths following i.v. administration to mice at a dose of 1000 mg/kg. Another exemplified compound is:



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INDICATION – Female contraception.

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SOURCE – Organon.

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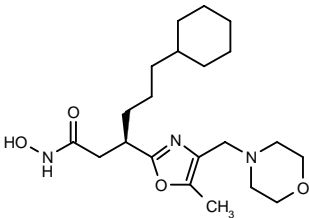
6. *NuvaRing launched as first vaginal birth control ring.* DailyDrugNews.com (Daily Essentials) 2002, July 19.

DERMATOLOGIC DRUGS

WOUND-HEALING AGENTS

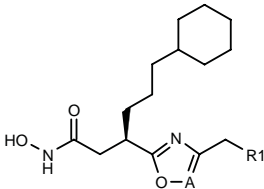
323352

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323355	NH2	N	C ₁₅ H ₂₆ N ₄ O ₃
323356	cyclopentyl-NH	N	C ₂₀ H ₃₄ N ₄ O ₃
323357	4-THP-NH	N	C ₂₀ H ₃₄ N ₄ O ₄
323358	N(Me)CH2CONHMe	N	C ₁₉ H ₃₃ N ₅ O ₄
323359	4-morpholinyl	CH	C ₂₀ H ₃₃ N ₅ O ₄

SOURCE – Pfizer.

REFERENCES

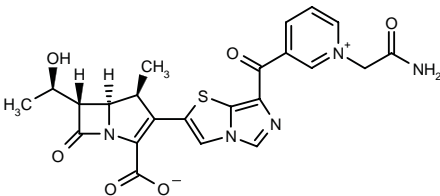
1. Datta, U. et al. (Pfizer Ltd.;Pfizer Inc.) *3-Ox(adi)azolylpropanohydroxamic acids useful as procollagen C-proteinase inhibitors.* WO 0250046.

ANTIINFECTIVE THERAPY

ANTIBIOTICS

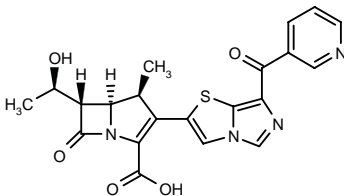
322446

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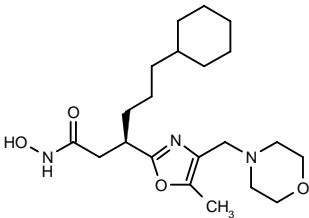
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DERMATOLOGIC DRUGS

WOUND-HEALING AGENTS

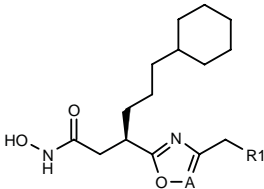
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323358	N(Me)CH2CONHMe	N	C ₁₉ H ₃₃ N ₅ O ₄
323359	4-morpholinyl	CH	C ₂₀ H ₃₃ N ₅ O ₄

SOURCE – Pfizer.

REFERENCES

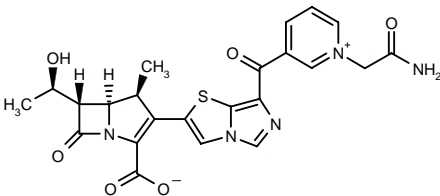
1. Datta, U. et al. (Pfizer Ltd.;Pfizer Inc.) *3-Ox(adi)azolylpropanohydroxamic acids useful as procollagen C-proteinase inhibitors.* WO 0250046.

ANTIINFECTIVE THERAPY

ANTIBIOTICS

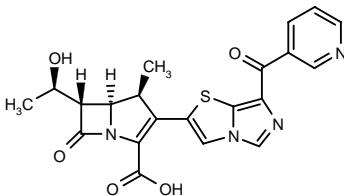
322446

(1R,5S,6S)-[2-[7-[1-(Carbamoylmethyl)pyridin-1-ium-3-ylcarbonyl]imidazo[5,1-*b*]thiazol-2-yl]-6-[1(R)-hydroxyethyl]-1-methyl-1-carba-2-penem-3-carboxylate



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ACTION – Carbapenem antibiotic with MIC values of < 0.1 µg/ml against a panel of bacterial strains. *In vivo*, it gave an ED₅₀ value of 0.07 mg/animal s.c. in mice with infections caused by methicillin-resistant *Staphylococcus aureus*. In acute toxicity tests, it caused no deaths following i.v. administration to mice at a dose of 1000 mg/kg. Another exemplified compound is:



322447: C21 H18 N4 O5 S

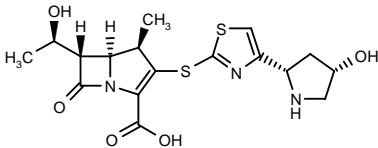
SOURCE – Meiji Seika.

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1. Kano, Y. et al. (Meiji Seika Kaisha, Ltd.) *Novel carbapenem derivs.* WO 0242312.

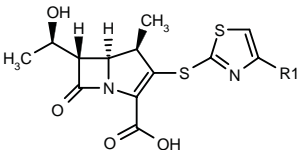
322580

(1*R*,5*S*,6*S*)-6-[1(*R*)-Hydroxyethyl]-2-[4-[4(*S*)-hydroxy-pyrrolidin-2(*S*)-yl]thiazol-2-ylsulfanyl]-1-methyl-1-carba-2-penem-3-carboxylic acid



C17 H21 N3 O5 S2; Mol wt: 411.5009

ACTION – Carbapenem antibiotic with potential in the treatment of infections caused by methicillin-resistant *Staphylococcus aureus* and coagulase-negative *Staphylococcus aureus*. Other exemplified compounds are:



Compound	R1	Formula
322581	4(R)-[N(Me)2CO]-2(S)-pyrrolidinyl	C ₂₀ H ₂₆ N ₄ O ₅ S ₂
322582	1-(NH=CH)-3(S)-pyrrolidinyl	C ₁₈ H ₂₂ N ₄ O ₄ S ₂
322583	1-[C(=NH)NH2]-3(S)-pyrrolidinyl	C ₁₈ H ₂₃ N ₅ O ₄ S ₂
322584	1-(NH=CH)-3(R)-pyrrolidinyl	C ₁₈ H ₂₂ N ₄ O ₄ S ₂
322585	1-[C(=NH)Me]-2(R)-pyrrolidinyl	C ₁₉ H ₂₄ N ₄ O ₄ S ₂
322587	1-[C(=NH)Me]-2(S)-pyrrolidinyl	C ₁₉ H ₂₄ N ₄ O ₄ S ₂
322588	5(S)-(AcOCH2)-1-[C(=NH)Me]-3(R)-pyrrolidinyl	C ₂₂ H ₂₈ N ₄ O ₆ S ₂

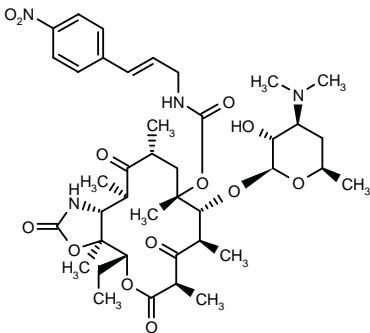
SOURCE – Sumitomo Pharmaceuticals.

REFERENCES

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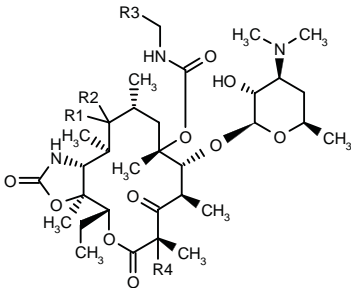
322796

11-Amino-11-deoxy-3-des(hexopyranosyloxy)-6-*O*-[*N*-[3-(4-nitrophenyl)-2(*E*)-propenyl]carbamoyl]-3-oxo-erythromycin A 11-*N*,12-*O*-cyclic carbamate



C40 H58 N4 O13; Mol wt: 802.9132

ACTION – Antibacterial ketolide with *in vitro* activity against *Escherichia coli* OC2605 (MIC = 4 µg/ml), *Staphylococcus aureus* ATCC29213 (MIC = 0.12 µg/ml), *Enterococcus faecalis* ATCC29212 (MIC = 0.06 µg/ml), *Streptococcus pneumoniae* ATCC49619 (MIC = 0.03 µg/ml) and *Haemophilus influenzae* ATCC49247 (MIC = 2 µg/ml). Potentially useful for the treatment of community-acquired pneumonia, upper and lower respiratory tract infections, skin and soft tissue infections, meningitis, hospital-acquired lung infections, and bone and joint infections. Other exemplified 6-*O*-carbamoyl erythromycin A derivatives include the following:



Compound	R1	R2	R3	R4	Formula
322797	-O-	-O-	(<i>E</i>)-6-Br-3-Pyr-CH=CH	H	C ₃₉ H ₅₇ BrN ₄ O ₁₁
322810	-O-	-O-	(<i>E</i>)-2-F-4-(1-imidazolyl)-PhCH=CH	H	C ₄₃ H ₆₀ FN ₅ O ₁₁
322811	-O-	-O-	4-(4-pyrimidinyl)-Ph	H	C ₄₂ H ₅₉ N ₅ O ₁₁
322812	-O-	-O-	5-(2-Pyr)-2-thienyl	H	C ₄₁ H ₅₈ N ₄ O ₁₁ S
322813	-O-	-O-	(<i>E</i>)-4-(3-pyridazinyl)-PhCH=CH	H	C ₄₄ H ₆₁ N ₅ O ₁₁
322814	N(OH)	-O-	(<i>E</i>)-3-quinolinyl-CH=CH	F	C ₄₃ H ₆₀ FN ₅ O ₁₁
322815	N(OH)	-O-	(<i>E</i>)-2-Br-4-Pyr-CH=CH	F	C ₃₉ H ₅₇ BrFN ₅ O ₁₁

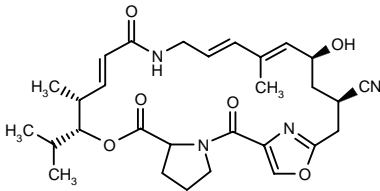
SOURCE – Ortho-McNeil.

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1. Henninger, T.C. and Xu, X.C. (Ortho-McNeil Pharmaceutical, Inc.) *6-O-Carbamoyl ketolide derivs. of erythromycin useful as antibacterials.* WO 0246204.

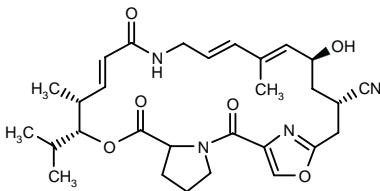
323516

(3*R*,4*R*,14*S*,16*R*)-14-Hydroxy-3-isopropyl-4,12-dimethyl-1,7,22-trioxo-3,4,7,8,9,14,15,16,17,22,24,25,26,26a-tetradecahydro-1*H*-21,18-epiazenopyrrolo[2,1-*c*]-[1,8,4,19]dioxadiazacyclotetracosine-16-carbonitrile



C29 H38 N4 O6; Mol wt: 538.6412

ACTION – Streptogramin derivative with antibacterial activity. Another exemplified compound is:



323517: C29 H38 N4 O6

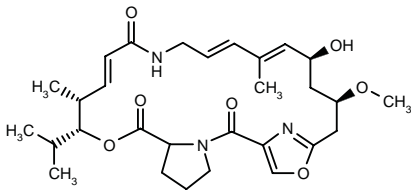
SOURCE – Aventis Pharma.

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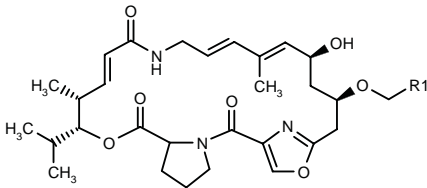
323519

(3*R*,4*R*,14*S*,16*R*)-14-Hydroxy-3-isopropyl-16-methoxy-4,12-dimethyl-3,4,7,8,9,14,15,16,17,22,24,25,26,26a-tetradecahydro-1*H*-21,18-epiazenopyrrolo[2,1-*c*]-[1,8,4,19]dioxadiazacyclotetracosine-1,7,22-trione

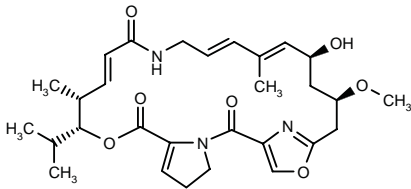


C29 H41 N3 O7; Mol wt: 543.6569

ACTION – Streptogramin derivative with antibacterial activity. Other exemplified compounds include the following:



Compound	R1	Formula
323520	vinyl	C ₃₁ H ₄₃ N ₃ O ₇
323521	ethynyl	C ₃₁ H ₄₁ N ₃ O ₇



323523: C29 H39 N3 O7

SOURCE – Aventis Pharma.

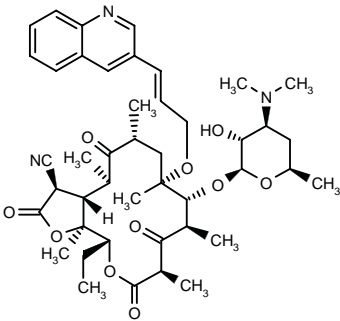
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1. Desmazeau, P. et al. (Aventis Pharma SA) *Streptogramin derivs., preparation thereof and compsns. containing same*. FR 2818644, WO 0250083.

323550

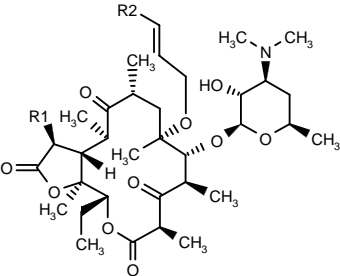
(3*aS*,4*R*,6*R*,8*R*,9*R*,10*R*,12*R*,15*R*,15*aS*)-9-[3-(Dimethylamino)-3,4,6-trideoxy-β-*D*-xylo-hexopyranosyloxy]-15-ethyl-4,6,8,10,12,15*a*-hexamethyl-2,5,11,13-tetraoxo-8-[3-(3-quinoliny)-2-propenyloxy]perhydrofuro-[2,3-*c*]oxacyclotetradecin-3-carbonitrile

(11*S*,21*R*)-11,12-Dideoxy-3-des(hexopyranosyloxy)-3-oxo-11,12-[1-(oxycarbonyl)-1-cyanomethylene]-6-*O*-[3-(3-quinoliny)-2-propenyl]erythromycin A



C44 H59 N3 O10; Mol wt: 789.9611

ACTION – Macrolide antibiotic that displayed MIC values in the range of 0.1-64 µg/ml against erythromycin-resistant *Streptococcus pneumoniae* strains. Other specifically claimed erythromycin A derivatives include the following:



Compound	R1	R2	Formula
323551	H	3-quinoliny	C ₄₃ H ₆₀ N ₂ O ₁₀
323553	CN	5-quinoliny	C ₄₄ H ₅₉ N ₃ O ₁₀
323554	CN	6-quinoliny	C ₄₄ H ₅₉ N ₃ O ₁₀
323555	CN	7-quinoliny	C ₄₄ H ₅₉ N ₃ O ₁₀

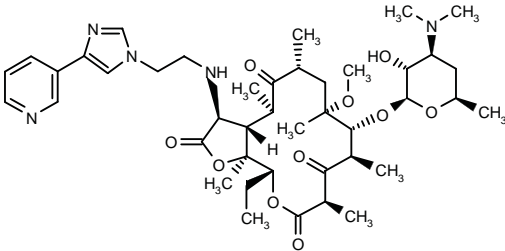
SOURCE – GlaxoSmithKline.

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1. Andreotti, D. et al. (GlaxoSmithKline plc) *Macrolide antibiotics*. WO 0250092.

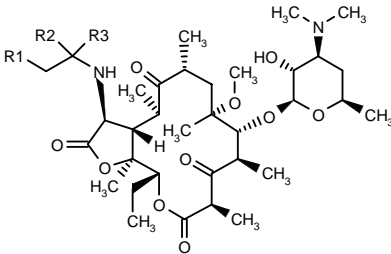
323559

(11*S*,21*S*)-11,12-Dideoxy-3-des(hexopyranosyloxy)-6-*O*-methyl-3-oxo-12,11-[1-(oxycarbonyl)-1-[2-[4-(3-pyridyl)-1*H*-imidazol-1-yl]ethylamino]methylene]erythromycin A



C42 H63 N5 O10; Mol wt: 797.9847

ACTION – Macrolide antibiotic that displayed MIC values in the range of 0.06-8 µg/ml against erythromycin-resistant *Streptococcus pneumoniae* strains. Other specifically claimed erythromycin A derivatives include the following:



Compound	R1	R2	R3	Formula
323561	4-quinolyl	H	H	C ₄₃ H ₆₃ N ₃ O ₁₀
323562	4-(3-Pyr)-1-imidazolyl-CH2	H	H	C ₄₃ H ₆₅ N ₅ O ₁₀
323563	2-quinoxaliny-S	-O-	-O-	C ₄₂ H ₆₀ N ₄ O ₁₁ S
323564	1,4-benzodioxan-6-yl-COCH2	-O-	-O-	C ₄₄ H ₆₄ N ₂ O ₁₄
323565	4-MeO-3-NO2-PhCOCH2	-O-	-O-	C ₄₃ H ₆₃ N ₃ O ₁₅
323566	2-OH-4,5-(MeO)2-PhCOCH2	-O-	-O-	C ₄₄ H ₆₆ N ₂ O ₁₅
323567	3,4-(MeO)2-PhCOCH2	-O-	-O-	C ₄₄ H ₆₆ N ₂ O ₁₄
323568	4-(2-thienyl)-1-imidazolyl-CH2	H	H	C ₄₂ H ₆₄ N ₄ O ₁₀ S

SOURCE – GlaxoSmithKline.

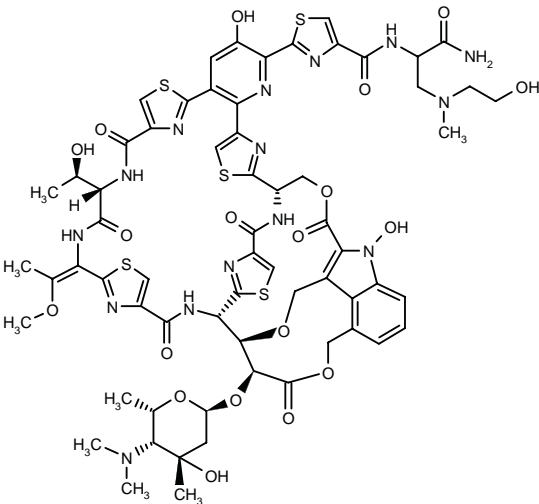
REFERENCES

1. Andreotti, D. et al. (GlaxoSmithKline plc) *Macrolide antibiotics*. WO 0250091.

BMS-411886

323673

N-[1-Carbamoyl-2-[*N*-(2-hydroxyethyl)-*N*-methyl-amino]ethyl]-2-[(1*S*,18*S*,21*E*,28*S*,29*R*,30*S*)-30-[(2*S*,4*S*,5*R*,6*S*)-5-(dimethylamino)-4-hydroxy-4,6-dimethyltetrahydropyran-2-yloxy]-9,52-dihydroxy-18-[1(*R*)-hydroxyethyl]-21-(1-methoxyethylidene)-16,19,26,31,42,46-hexaoxo-32,43,54-trioxa-3,13,23,49-tetrathia-7,17,20,27,45,51,52,55,56,57-deca-azadecacyclo[26.16.6.2^{29,40}).1^{2,5}.1^{12,15}.1^{22,25}.1^{38,41}.1^{47,50}.0^{6,11}.0^{34,39}]heptapentaconta-2(57),4,6,8,10,12(56),14,22(55),24,34,36,38,40,47,50-pentadecaen-8-yl]thiazole-4-carboxamide



C64 H69 N15 O19 S5; Mol wt: 1512.6650

ACTION – Antibacterial agent, a derivative of nocathiacin I, a macrocyclic compound isolated from *Nocardia* sp. with potent antibacterial activity against clinically relevant Gram-positive bacteria but extremely low solubility. Compound exhibits improved solubility and retains the antimicrobial potency of nocathiacin I; it showed *in vivo* efficacy following i.v. administration to mice (PD₅₀ = 0.24 mg/kg).

SOURCE – Bristol-Myers Squibb.

REFERENCES

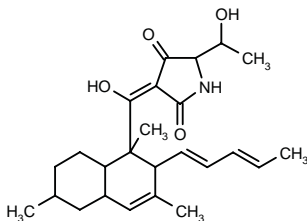
1. Naidu, B.N. et al. (Bristol-Myers Squibb Co.) *Water soluble thiazolyl peptide derivs*. WO 0214354.

2. Naidu, B.N. et al. *Synthesis and antibacterial activity of novel nocathiacin I analogs*. 224th ACS Natl Meet (Aug 18-22, Boston) 2002, Abst MEDI 209.

CONIOSETIN

322764

5-(1-Hydroxyethyl)-3-[1-hydroxy-1-[1,3,6-trimethyl-2-(1,3-pentadienyl)-1,2,4a,5,6,7,8,8a-octahydronaphthalen-1-yl]methylene]pyrrolidine-2,4-dione



C25 H35 N O4; Mol wt: 413.5545

ACTION – Antibiotic isolated from cultures of *Coniochaeta ellipsoidea* Udagawa (DSM 13856) and described as useful for the treatment of bacterial and fungal infections. Coniosetin exhibited *in vitro* activity against *Staphylococcus aureus*, *Candida albicans*, *Streptomyces murinus* and *Aspergillus niger*.

SOURCE – Aventis Pharma.

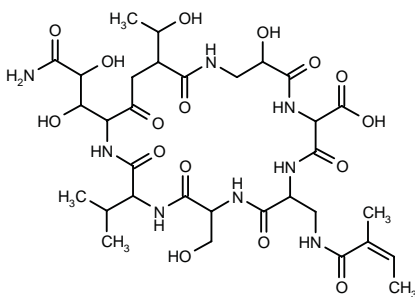
REFERENCES

1. Vertesy, L. et al. (Aventis Pharma Deutschland GmbH) *Coniosetin and derivs. thereof, method for producing the same and use thereof*. DE 10060810, WO 0246152.

GE-23077-A1

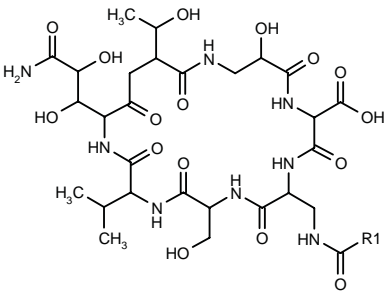
322674

22-(2-Carbamoyl-1,2-dihydroxyethyl)-15-hydroxy-19-(1-hydroxyethyl)-6-(hydroxymethyl)-3-isopropyl-9-[2-methyl-2(*Z*)-butenamidomethyl]-2,5,8,11,14,18,21-heptaoxo-1,4,7,10,13,17-hexaazacyclodocosane-12-carboxylic acid isomer A



C32 H50 N8 O16; Mol wt: 802.7870

ACTION – A component of the antibacterial complex GE-23077 isolated from cultures of the fungus *Actinomadura* sp. DSMZ 13491. GE-23077-A1 inhibited *Escherichia coli* RNA polymerase with an IC₅₀ of 0.15 µg/ml. It is reported to be active *in vitro* against *Moraxella catarrhalis*. Other constituents of the GE-23077 complex are:



Compound	R1	Isomer	Formula
GE-23077-A2 [322675]	(<i>Z</i>)-C(Me)=CHMe	B	C ₃₂ H ₅₀ N ₈ O ₁₆
GE-23077-B1 [322676]	i-Bu	A	C ₃₂ H ₅₂ N ₈ O ₁₆
GE-23077-B2 [322677]	i-Bu	B	C ₃₂ H ₅₂ N ₈ O ₁₆

SOURCE – Biosearch Italia.

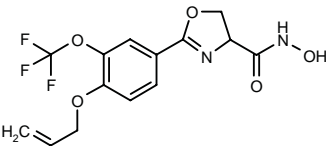
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ANTIBACTERIAL DRUGS

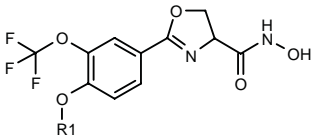
321500

2-[4-(Allyloxy)-3-(trifluoromethoxy)phenyl]-4,5-dihydro-oxazole-4-carboxydroxamic acid



C14 H13 F3 N2 O5; Mol wt: 346.2597

ACTION – *Pseudomonas aeruginosa* deacetylase LpxC inhibitor (IC₅₀ = 0.12 µM), potentially useful as an antibacterial agent for Gram-negative microorganisms. Other related compounds are:



Compound	R1	Formula
321499	Me	C ₁₂ H ₁₁ F ₃ N ₂ O ₅
321501	CH2CH=C(Me)2	C ₁₆ H ₁₇ F ₃ N ₂ O ₅

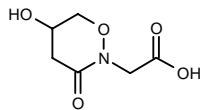
SOURCE – Chiron.

REFERENCES

1. Kline, T. et al. *Potent, novel in vitro inhibitors of the Pseudomonas aeruginosa deacetylase LpxC*. J Med Chem 2002, 45(14): 3112.

322439

2-(5-Hydroxy-3-oxoperhydro-1,2-oxazin-2-yl)acetic acid



C6 H9 N O5; Mol wt: 175.1391

ACTION – A representative compound from a series of antibacterial oxazinones with the ability to bind to penicillin receptors, thus interfering with the formation of the bacterial cell wall. Compound inhibited the growth of *Micrococcus luteus* in an agar diffusion assay.

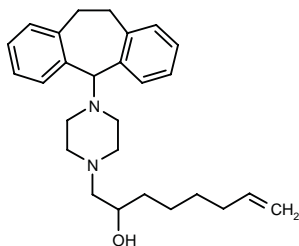
SOURCE – Simon Fraser University, Burnaby (CA).

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1. Wolfe, S. et al. (Simon Fraser University) *Oxazinones having antibacterial activity*. US 6399600.

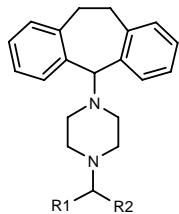
322569

1-[4-(10,11-Dihydro-5*H*-dibenzo[*a,d*]cyclohepten-5-yl)-piperazin-1-yl]-7-octen-2-ol



C27 H36 N2 O; Mol wt: 404.5944

ACTION – Agent with the ability to reverse drug resistance of microorganisms such as *Mycobacterium tuberculosis*, *Escherichia coli*, *Plasmodium*, *Leishmania* parasites, etc. It was shown to completely reverse chloroquine resistance of a *Plasmodium chabaudi* strain when administered to infected mice at a dose of 50 mg/kg i.p. Other exemplified compounds are:



Compound	R1	R2	Formula
322570	CH(OH)(CH2)6CH=CH2	H	C ₂₉ H ₄₀ N ₂ O
322571	CH(OH)CH2CH2CH=CH2	H	C ₂₅ H ₃₂ N ₂ O
322572	CH(OH)CH=CH2	H	C ₂₃ H ₂₈ N ₂ O
322573	vinyl	CH2OH	C ₂₃ H ₂₈ N ₂ O
322574	CH(OH)(CH2)7Me	H	C ₂₉ H ₄₂ N ₂ O

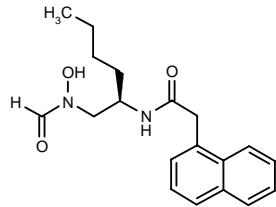
SOURCE – Pola Chemical.

REFERENCES

1. Takeuchi, T. et al. (Pola Chemical Industries Inc.) *Dibenzosuberanyl piperazine derivs. and drug-resistance overcoming agents containing the derivs.*. WO 0242284.

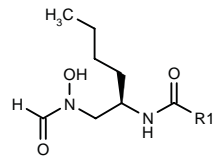
323402

N-[1(*R*)-(N-Formyl-N-hydroxyaminomethyl)pentyl]-2-(1-naphthyl)acetamide

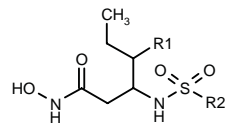


C19 H24 N2 O3; Mol wt: 328.4096

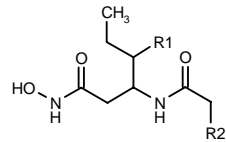
ACTION – Antimicrobial agent with antibacterial and antiprotozoal activity that acts at least in part through inhibition of bacterial polypeptide deformylase. Other exemplified compounds include the following:



Compound	R1	Formula
323403	1-cyclohexyl-4-oxo-1,4-dihydro-3-quinolinyl	C ₂₃ H ₃₁ N ₃ O ₄
323404	4-oxo-1-benzopyran-3-yl	C ₁₇ H ₂₀ N ₂ O ₅



Compound	R1	R2	Isomer	Formula
323405	H	2,1,3-benzothiadiazol-4-yl		C ₁₂ H ₁₆ N ₄ O ₄ S ₂
323409	Me	3,4-(Cl)2-Ph	3(R),4(S)	C ₁₃ H ₁₈ Cl ₂ N ₂ O ₄ S



Compound	R1	R2	Isomer	Formula
323407	H	2-Me-5-MeO-3-indolyl		C ₁₈ H ₂₅ N ₃ O ₄
323408	H	1-Naph		C ₁₈ H ₂₂ N ₂ O ₃
323411	Me	2-Me-5-MeO-3-indolyl	3(R),4(S)	C ₁₉ H ₂₇ N ₃ O ₄
323412	Me	1-Naph	3(R),4(S)	C ₁₉ H ₂₄ N ₂ O ₃

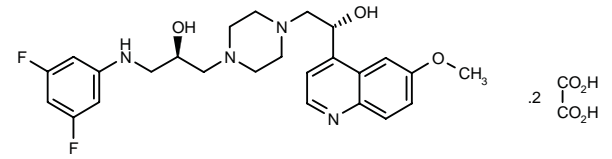
SOURCE – De Novo Pharmaceuticals.

REFERENCES

1. Porter, B. et al. (De Novo Pharmaceuticals Ltd.) *Antimicrobial agents*. WO 0250081.

323435

1-(3,5-Difluorophenylamino)-3-[4-[2(*R*)-hydroxy-2-(6-methoxyquinolin-4-yl)ethyl]piperazin-1-yl]propan-2(*R*)-ol dioxalate



C25 H30 F2 N4 O3 . 2 C2 H2 O4; Mol wt: 652.6006

ACTION – Antibacterial agent displaying MIC values below 1 µg/ml when tested *in vitro* against *Staphylococcus aureus* Oxford, *S. aureus* WCUH29 and *Streptococcus pneumoniae* 1629, N1387 and ERY2 strains. Other exemplified piperazine derivatives are:

Compound	R1	X	Formula
323436	3,5-(F)2-PhNHCH2CH(OH)		C ₂₅ H ₃₀ F ₂ N ₄ O ₃
323437	3-[3,5-(F)2-Ph]-2-oxo-5-oxazolidinyl	2MeSO3H	C ₂₆ H ₂₈ F ₂ N ₄ O ₄ .2CH ₄ O ₃ S
323438	CH2NHCOPh	dioxalate	C ₂₅ H ₃₀ N ₄ O ₃ .2C ₂ H ₂ O ₄
323439	3,5-(F)2-PhCONHCH2	dioxalate	C ₂₅ H ₂₈ F ₂ N ₄ O ₃ .2C ₂ H ₂ O ₄
323440	2-thienyl-CONHCH2	dioxalate	C ₂₃ H ₂₈ N ₄ O ₃ S.2C ₂ H ₂ O ₄
323441	(CH2)3Ph	dioxalate	C ₂₆ H ₃₃ N ₃ O ₂ .2C ₂ H ₂ O ₄
323442	3,5-(F)2-PhNHCOCH2	dioxalate	C ₂₅ H ₂₈ F ₂ N ₄ O ₃ .2C ₂ H ₂ O ₄
323443	3-(3-F-Ph)-2-oxo-5-oxazolidinyl	2MeSO3H	C ₂₆ H ₂₉ FN ₄ O ₄ .2CH ₄ O ₃ S
323457	CH(OH)CH2OPh	dioxalate	C ₂₅ H ₃₁ N ₃ O ₄ .2C ₂ H ₂ O ₄

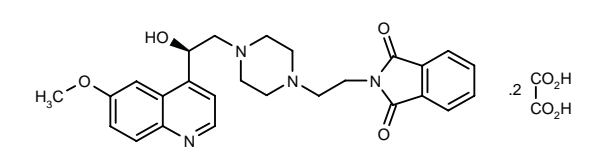
SOURCE – GlaxoSmithKline.

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323487

2-[2-[4-[2(*R*)-Hydroxy-2-(6-methoxyquinolin-4-yl)-ethyl]piperazin-1-yl]ethyl]-2,3-dihydro-1*H*-isoindole-1,3-dione dioxalate



C26 H28 N4 O4 . 2 C2 H2 O4; Mol wt: 640.5988

ACTION – Antibacterial agent that demonstrated *in vitro* activity against *Staphylococcus aureus* Oxford, *S. aureus* WCUH29, *Streptococcus pneumoniae* 1629, N1387 and ERY 2 strains, *Haemophilus influenzae* Q1 and *Enterococcus faecalis* 7. Other exemplified piperazine derivatives include the following:

Compound	R1	X	Formula
323488	4-F-2-benzimidazolyl-CH2		C ₂₅ H ₂₈ FN ₅ O ₂
323490	5-F-2-benzimidazolyl-CH2		C ₂₅ H ₂₈ FN ₅ O ₂
323497	1,4-benzodioxan-6-yl-CH(OH)	3HCl	C ₂₆ H ₃₁ N ₃ O ₅ .3HCl

Compound	R1	X	Formula
323489	4-F-2-benzimidazolyl-CH2		C ₂₃ H ₂₄ FN ₇ O ₂
323491	1,4-benzodioxan-6-yl-CH2	dioxalate	C ₂₄ H ₂₇ N ₅ O ₄ .2C ₂ H ₂ O ₄
323492	1,3-benzodioxol-5-yl-CH2	dioxalate	C ₂₃ H ₂₅ N ₅ O ₄ .2C ₂ H ₂ O ₄
323493	3-oxo-3,4-dihydro-2H-1,4-benzothiazin-6-yl-CH2		C ₂₄ H ₂₈ N ₆ O ₃ S
323494	2-quinoxaliny-CH2		C ₂₄ H ₂₈ N ₇ O ₂
323495	2,1,3-benzothiadiazol-5-yl-CH2		C ₂₂ H ₂₃ N ₇ O ₂ S
323496	3,4-dihydro-3-oxo-2H-1,4-benzoxazin-6-yl-CO		C ₂₄ H ₂₄ N ₆ O ₅

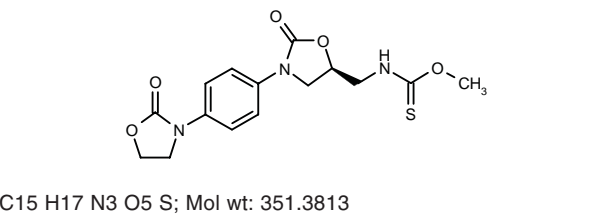
SOURCE – GlaxoSmithKline.

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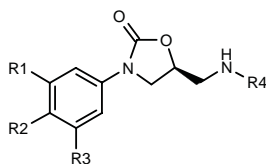
323739

N-[2-Oxo-3-[4-(2-oxooxazolidin-3-yl)phenyl]oxazolidin-5(*S*)-ylmethyl]thiocarbamic acid *O*-methyl ester



C15 H17 N3 O5 S; Mol wt: 351.3813

ACTION – Antibacterial agent giving MIC values of 0.5 µg/ml against several strains of *Staphylococcus aureus*, 1.0 µg/ml against *Enterococcus faecalis* and *Enterococcus faecium*, and 32.0 µg/ml against *Escherichia coli*. Other exemplified heterocyclic compounds are:



Compound	R1	R2	R3	R4	Formula
323740	F	2-oxo-3-oxazolidinyl	H	Ac	C ₁₅ H ₁₆ FN ₃ O ₅
323741	H	2-oxo-3-oxazolidinyl	H	Ac	C ₁₅ H ₁₇ N ₃ O ₅
323742	F	2-oxo-3-oxazolidinyl	F	CSMe	C ₁₅ H ₁₅ F ₂ N ₃ O ₄ S
323743	F	3-Me-2-oxo-1-imidazolidinyl	H	CSMe	C ₁₆ H ₁₉ FN ₄ O ₃ S
323744	F	2-oxo-3-oxazolidinyl	H	CSOMe	C ₁₅ H ₁₆ FN ₃ O ₅ S
323745	F	2-oxo-3-oxazolidinyl	H	CSOEt	C ₁₆ H ₁₈ FN ₃ O ₅ S
323746	F	2-oxo-3-oxazolidinyl	F	CSOMe	C ₁₅ H ₁₅ F ₂ N ₃ O ₅ S
323747	H	2-oxo-3-oxazolidinyl	H	i-PrOCS	C ₁₇ H ₂₁ N ₃ O ₅ S
323748	F	3-Me-2-oxo-1-imidazolidinyl	H	CSOMe	C ₁₆ H ₁₉ FN ₄ O ₄ S
323749	F	3-(OHCH2)-4-oxo-1-imidazolidinyl	H	CSOMe	C ₁₆ H ₁₉ FN ₄ O ₅ S
323750	F	4-oxo-1-imidazolidinyl	H	CSOMe	C ₁₅ H ₁₇ FN ₄ O ₄ S
323751	F	3-(MeOCH2)-4-oxo-1-imidazolidinyl	H	CSOMe	C ₁₇ H ₂₁ FN ₄ O ₅ S

SOURCE – Dr. Reddy’s Research Foundation.

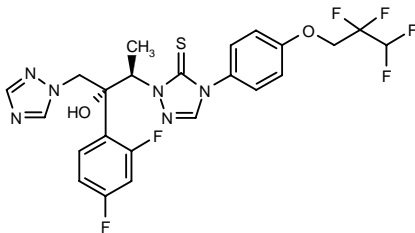
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ANTIFUNGAL AGENTS

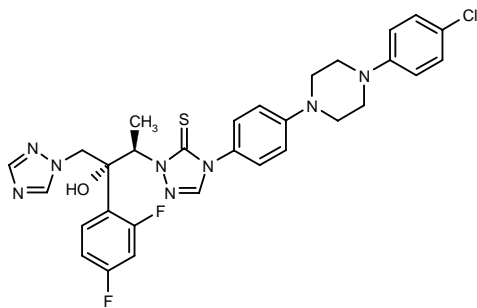
323627

2-[2(R)-(2,4-Difluorophenyl)-2-hydroxy-1(R)-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]-4-[4-(2,2,3,3-tetrafluoropropoxy)phenyl]-3,4-dihydro-2H-1,2,4-triazole-3-thione



C23 H20 F6 N6 O2 S; Mol wt: 558.5050

ACTION – Antifungal agent described as useful for the treatment of topical fungal infections caused by *Candida*, *Trichophyton*, *Microsporum* and *Epidermophyton* species, mucosal infections caused by *Candida albicans*, and systemic fungal infections associated with *Candida* spp., *Cryptococcus neoformans*, *Aspergillus fumigatus*, *Fusarium*, *Rhizopus* and *Penicillium marneffe*i. The compound demonstrated *in vitro* activity against a wide panel of fungal pathogens, with MIC values comparable to or better than those of amphotericin B, fluconazole, itraconazole and TAK-187. *In vivo*, it protected mice from *A. fumigatus* infection with ED₅₀ values of 2.33 and 6.25 mg/kg, respectively, when measured 7 and 14 days after infection. Another exemplified substituted azole derivative is:



323763: C30 H29 Cl F2 N8 O S

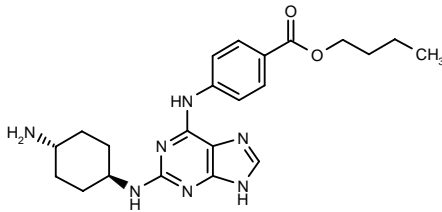
SOURCE – Ranbaxy.

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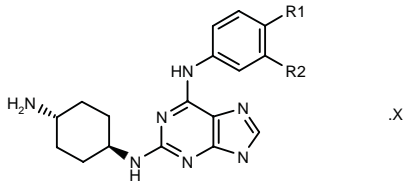
323778

trans-4-[2-(4-Aminocyclohexylamino)-9H-purin-6-yl-amino]benzoic acid butyl ester



C22 H29 N7 O2; Mol wt: 423.5181

ACTION – Antifungal agent that acts by inhibiting the *Candida albicans* protein kinase CIV1 (IC₅₀ = 5.6 μM). Compound exhibited an MIC value of 12.5 μg/ml against *C. albicans*. Other exemplified purine derivatives are:



Compound	R1	R2	X	Formula
323779	CO2Et	H	2HCl	C ₂₀ H ₂₅ N ₇ O ₂ ·2HCl
323780	H	H	2HCl	C ₁₇ H ₂₁ N ₇ ·2HCl
323781	H	CO2Et		C ₂₀ H ₂₅ N ₇ O ₂
323782	Cl	H		C ₁₇ H ₂₀ ClN ₇
323783	CO2CH2CH2N(Et)2	H		C ₂₂ H ₃₀ N ₈ O ₂
323784	CONHPh	H		C ₂₄ H ₂₆ N ₈ O

SOURCE – Aventis Pharma.

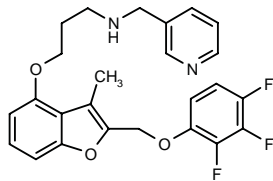
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RO-0094879*

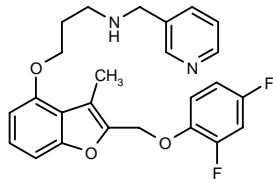
311281

N-[3-[3-Methyl-2-(2,3,4-trifluorophenoxy)methyl]-1-benzofuran-4-yloxy]propyl]-N-(pyridin-3-ylmethyl)amine



C25 H23 F3 N2 O3; Mol wt: 456.4617

ACTION – Antifungal agent, a potent and selective inhibitor of *Candida albicans* N-myristoyltransferase (IC₅₀ = 5.7 nM and > 430 μM against *C. albicans* and human enzyme, respectively). Compound exhibited strong antifungal activity against *C. albicans* *in vitro* (IC₅₀ = 0.035 μM) and *in vivo* in a systemic murine candidiasis model (ED₅₀ = 7.1 mg/kg i.v.). Another related compound is:



Ro-0094746 [311280]**: C25 H24 F2 N2 O3

SOURCE – Nippon Roche.

REFERENCES

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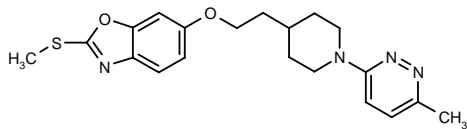
*Identified compound **311281** (see **311280**) Drug Data Rep 2002, 024(01): 0063.

Identified compound **311280 Drug Data Rep 2002, 024(01): 0063.

ANTIVIRAL DRUGS

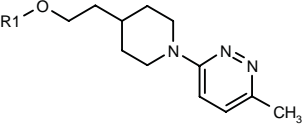
323383

6-[2-[1-(6-Methylpyridazin-3-yl)piperidin-4-yl]ethoxy]-2-(methylsulfanyl)benzoxazole



C20 H24 N4 O2 S; Mol wt: 384.5016

ACTION – Agent for the treatment of picornaviral infections, particularly rhinovirus infections, shown to protect MRC-5 cells from the cytopathic effects of human rhinovirus HRV1A, HRV2 and HRV14 with respective IC₅₀ values of 0.006, 0.099 and 0.047 μg/ml. In cytotoxicity assays, compound gave a CC₅₀ value of > 1 μg/ml. Other exemplified compounds are:



Compound	R1	Formula
323384	2-Me-6-benzoxazolyl	C ₂₀ H ₂₄ N ₄ O ₂
323385	2-Me-5-benzoxazolyl	C ₂₀ H ₂₄ N ₄ O ₂
323386	2-Et-6-benzoxazolyl	C ₂₁ H ₂₆ N ₄ O ₂

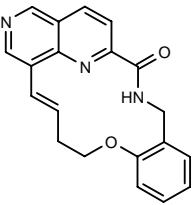
SOURCE – Biota Scientific Management.

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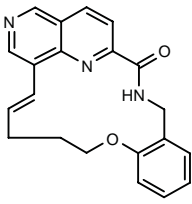
323624

8,9,15,16-Tetrahydro-7H-4,6-ethenopyrido[3,4-f][1,8,11]-benzoxadiazacyclotetradecin-7-one



C20 H17 N3 O2; Mol wt: 331.3733

ACTION – Macrocyclic antiviral compound that demonstrated *in vitro* activity against herpes simplex virus (HSV), Epstein-Barr virus (EBV), varicella-zoster virus (VZV) and cytomegalovirus (CMV). Another exemplified compound is:



323625: C21 H19 N3 O2

SOURCE – Shire BioChem.

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1. Falardeau, G. et al. (Shire BioChem Inc.) *Macrocyclic anti-viral cpds.* WO 0251413.

CARRAGUARD™

289579

3% Carrageenan gel

PC-515

ACTION – Carrageenan-based gel formulation with microbicidal activity against HIV, herpes simplex virus type 2 (HSV-2), human papillomavirus (HPV) and gonorrhea. Preclinical studies showed that carrageenan bound to the vaginal epithelium for 4 h and retained complete activity for 3 h after application; the gel had no harmful effects on the vaginal tissue of rabbits. Significant amounts of carrageenan could be detected in women up to 24 h after application. Results of phase II clinical trials in HIV-negative female patients from Thailand and South Africa showed that application of the gel was well tolerated by women and no significant differences compared to the placebo gel were seen in terms of genital irritation or abnormalities.

SOURCE – Population Council.

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7. Jones, H. et al. Vaginal product use by phase II microbicide trial participants in South Africa. 14th Int AIDS Conf (July 7-12, Barcelona) 2002, Abst MoPeD3653.

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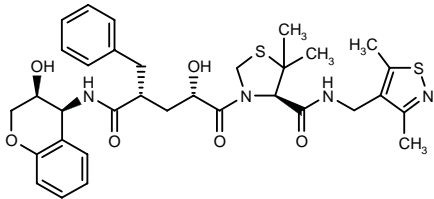
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AIDS MEDICINES

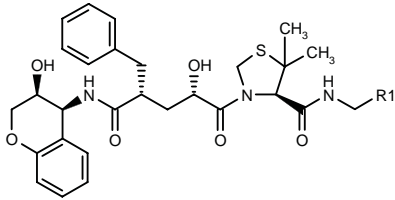
323663

N-(3,5-Dimethylisothiazol-4-ylmethyl)-3-[2(*S*)-hydroxy-4(*R*)-[*N*-[3(*S*)-hydroxy-3,4-dihydro-2*H*-1-benzopyran-4(*S*)-yl]carbamoyl]-5-phenylpentanoyl]-5,5-dimethylthiazolidine-4(*R*)-carboxamide



C33 H40 N4 O6 S2; Mol wt: 652.8330

ACTION – Potent HIV protease inhibitor (IC₅₀ = 0.045 and 0.11 nM against wild-type and mutant enzymes, respectively), a hybrid compound combining the structure of indinavir and JE-2147 with improved potency compared to indinavir. Compound was able to inhibit the spread of HIV-1 infection in human T-lymphoid cells with IC₅₀ values of 70.31 and 31.25 nM in wild-type and mutant isolates, respectively. Other related compounds are:



Compound	R1	Formula
323661	2,6-(Me)2-Ph	C ₃₆ H ₄₃ N ₃ O ₆ S
323662	3,5-(Me)2-4-isoxazolyl	C ₃₃ H ₄₀ N ₄ O ₇ S

SOURCE – Merck & Co.

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2. Lu, Z. et al. Design and synthesis of highly potent HIV protease inhibitors with activity against protease resistant virus. 224th ACS Natl Meet (Aug 18-22, Boston) 2002, Abst MEDI 205.

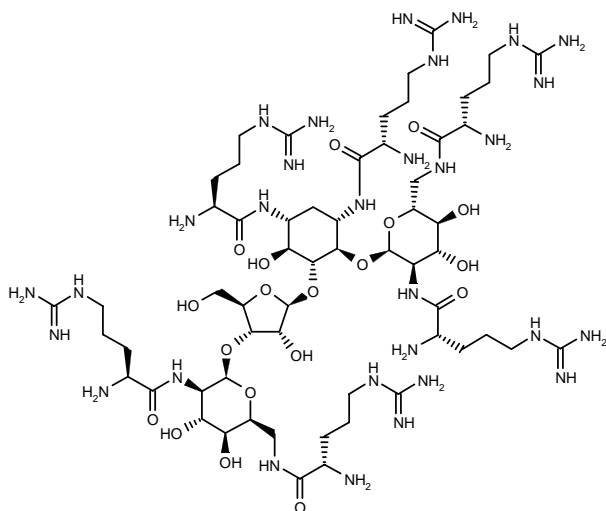
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NEOMYCIN B-ARGININE CONJUGATE

291465

N^1, N^3 -Bis(L-arginyl)-O-2,6-bis(L-arginylamino)-2,6-dideoxy- α -D-glucopyranosyl-(1 \rightarrow 4)-[O-2,6-bis(L-arginylamino)-2,6-dideoxy- β -L-idopyranosyl-(1 \rightarrow 3)- β -D-ribofuranosyl-(1 \rightarrow 5)]-2-deoxy-D-streptamine

Neomycin B-hexaarginine conjugate
NeoR



C59 H118 N30 O19; Mol wt: 1551.7720

ACTION – Anti-HIV agent, an aminoglycoside-arginine conjugate with up to 30-fold increased potency relative to previous aminoglycosides. It inhibited the replication of HIV-1 strains including zidovudine (AZT)-resistant strains (IC_{50} = 0.73-4 μ M), with no cytotoxicity up to 55 μ M. The conjugate inhibited HIV-1 binding to cells partially by blocking the CXCR4 HIV-1 coreceptor and antagonized Tat intracellular and extracellular functions.

SOURCE – Yeda.

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PERTUSSIS TOXIN B-OLIGOMER

322554

B-oligomer (binding subunit) of pertussis toxin

PTX-B

ACTION – Anti-HIV agent, the binding subunit of pertussis toxin (PTX-B) proven to inhibit HIV-1 infection at both the entry and the postentry stages of viral replication. Compound deactivates the chemokine CCR5 receptor and thereby blocks the entry of M-tropic HIV-1 strains into the host cell; it also suppressed HIV-1 RNA synthesis in cultures of infected peripheral blood mononuclear cells (PBMCs) when infection had been inhibited by zidovudine, and it affected the transcription of Tat-stimulated HIV-1 mRNA. In HIV-infected mice reconstituted with human PBMCs, compound completely inhibited viral infection in PBMCs migrated into lymph nodes and spleen, as well as plasma viremia and viral recovery from *ex vivo* PBMCs in 75% of animals.

SOURCES – Picower Institute for Medical Research, Manhasset, NY (US); San Raffaele Scientific Institute, Milano (IT).

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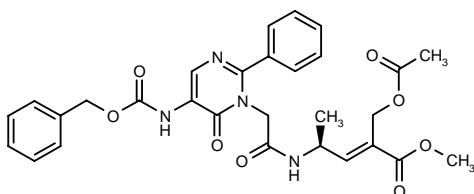
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TREATMENT OF PROTOZOAL DISEASES

323033

2-(Acetoxymethyl)-4(*S*)-[2-[5-(benzyloxycarbonylamino)-6-oxo-2-phenyl-1,6-dihydropyrimidin-1-yl]acetamido]-2-pentenoic acid methyl ester

N-[1-[*N*-[3-(Acetoxymethyl)-4-methoxy-1(*S*)-methyl-4-oxo-2-butenyl]carbamoylmethyl]-6-oxo-2-phenyl-1,6-dihydropyrimidin-5-yl]carbamic acid benzyl ester



C₂₉ H₃₀ N₄ O₈; Mol wt: 562.5760

ACTION – Antimalarial agent with potent *in vitro* growth-inhibitory activity against chloroquine-sensitive and -resistant *Plasmodium falciparum* strains (IC₅₀ = 9 and 10 ng/ml, respectively) and moderate to weak cytotoxicity against human cells (IC₅₀ > 1100 ng/ml). At doses of 40-160 mg/kg s.c., it prolonged the life span of *Plasmodium berghei*-infected mice from 6 days in control animals to 16-24 days.

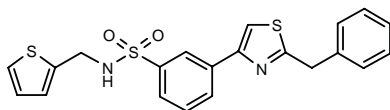
SOURCE – Walter Reed Army Institute, Washington, DC (US).

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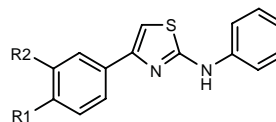
323634

3-(2-Benzylthiazol-4-yl)-*N*-(thien-2-ylmethyl)benzene-sulfonamide



C₂₁ H₁₈ N₂ O₂ S₃; Mol wt: 426.5832

ACTION – Agent for the treatment of parasitic infections, especially protozoal infections, that demonstrated *in vitro* activity against *Toxoplasma gondii* in a plaque assay at 25 μM. Potentially useful for the treatment of infections caused by *Eimeria* spp., *T. gondii*, *Neospora caninum* and *Cryptosporidium* spp. Other exemplified compounds are:



Compound	R1	R2	Formula
323635	H	SO ₂ N(Me)CH ₂ Ph	C ₂₃ H ₂₁ N ₃ O ₂ S ₂
323636	SO ₂ N(Me)CH ₂ Ph	H	C ₂₃ H ₂₁ N ₃ O ₂ S ₂
323637	SO ₂ NHPh	H	C ₂₁ H ₁₇ N ₃ O ₂ S ₂

SOURCE – Akzo Nobel.

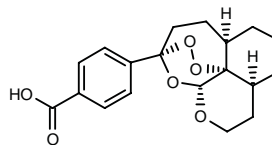
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HBJ-10

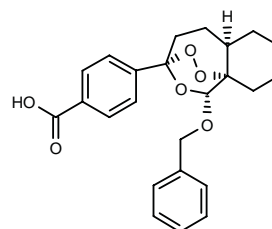
322987

4-[(3*S*,5*aR*,8*aS*,12*R*,12*aR*)-Perhydro-3,12-epoxy[1,2]dioxepino[4,3-*l*]-2-benzopyran-3-yl]benzoic acid



C₁₉ H₂₂ O₆; Mol wt: 346.3768

ACTION – Antimalarial agent, a water-soluble trioxane with oral efficacy against *Plasmodium berghei* infections in mice (ED₅₀ = 15 mg/kg, ED₉₀ = 51 mg/kg). Another related compound is:



HBJ-34a [322986]: C₂₄ H₂₆ O₆

SOURCE – Johns Hopkins University, Baltimore, MD (US).

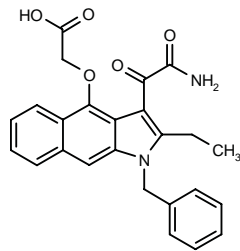
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TREATMENT OF SEPTIC SHOCK

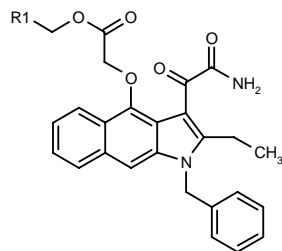
323461

2-(1-Benzyl-2-ethyl-3-oxamoyl-1*H*-benzo[*f*]indol-4-yloxy)-acetic acid



C25 H22 N2 O5; Mol wt: 430.4578

ACTION – Secretory phospholipase A₂ (sPLA₂) inhibitor (IC₅₀ = 1.06 μM), expected to be useful for the treatment of inflammatory disorders such as septic shock, inflammatory bowel disease, adult respiratory distress syndrome, pancreatitis, trauma, asthma, allergic rhinitis, rheumatoid arthritis, osteoarthritis, etc. Other exemplified compounds are:



Compound	R1	Formula
323463	Me	C ₂₇ H ₂₆ N ₂ O ₅
323464	Ph	C ₃₂ H ₂₈ N ₂ O ₅

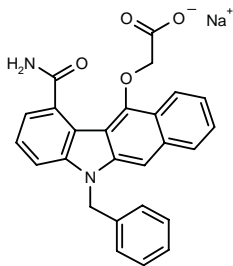
SOURCE – Lilly.

REFERENCES

1. Beight, D.W. et al. (Eli Lilly and Company) *Novel sPLA₂ inhibitors*. WO 0250028.

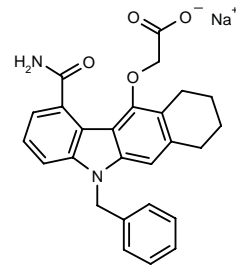
323466

2-(5-Benzyl-1-carbamoyl-5*H*-benzo[*b*]carbazol-11-yloxy)-acetic acid sodium salt



C26 H19 N2 Na O4; Mol wt: 446.4361

ACTION – Secretory phospholipase A₂ (sPLA₂) inhibitor (IC₅₀ = 38.6 μM), expected to be useful for the treatment of inflammatory disorders such as septic shock, inflammatory bowel disease, adult respiratory distress syndrome, pancreatitis, trauma, asthma, allergic rhinitis, rheumatoid arthritis, osteoarthritis, etc. Another exemplified compound is:



323467: C26 H23 N2 Na O4

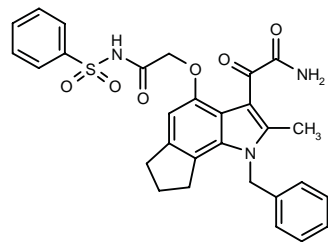
SOURCE – Lilly.

REFERENCES

1. Beight, D.W. et al. (Eli Lilly and Company) *Novel sPLA₂ inhibitors*. WO 0250029.

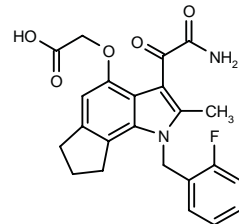
323468

2-[1-Benzyl-2-methyl-4-[*N*-(phenylsulfonyl)carbamoyl-methoxy]-1,6,7,8-tetrahydrocyclopenta[*g*]indol-3-yl]-2-oxoacetamide



C29 H27 N3 O6 S; Mol wt: 545.6133

ACTION – Secretory phospholipase A₂ (sPLA₂) inhibitor (IC₅₀ = 0.007 μM), expected to be useful for the treatment of inflammatory disorders such as septic shock, inflammatory bowel disease, adult respiratory distress syndrome, pancreatitis, trauma, asthma, allergic rhinitis, rheumatoid arthritis, osteoarthritis, etc. Another exemplified compound is:



323469: C23 H21 F N2 O5

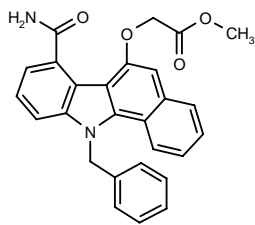
SOURCE – Lilly.

REFERENCES

1. Beight, D.W. et al. (Eli Lilly and Company) *Novel sPLA₂ inhibitors*. WO 0250030.

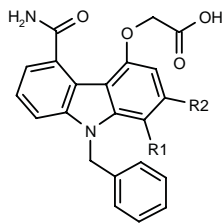
323470

2-(11-Benzyl-7-carbamoyl-11 *H*-benzo[*a*]carbazol-6-yloxy)acetic acid methyl ester



C27 H22 N2 O4; Mol wt: 438.4808

ACTION – Secretory phospholipase A₂ (sPLA₂) inhibitor (IC₅₀ = 38.6 μM), expected to be useful for the treatment of inflammatory disorders such as septic shock, inflammatory bowel disease, adult respiratory distress syndrome, pancreatitis, trauma, asthma, allergic rhinitis, rheumatoid arthritis, osteoarthritis, etc. Other exemplified compounds are:



Compound	R1	R2	Formula
323471		-(CH2)4-	C ₂₆ H ₂₄ N ₂ O ₄
323472		-(CH2)3-	C ₂₅ H ₂₂ N ₂ O ₄

SOURCE – Lilly.

REFERENCES

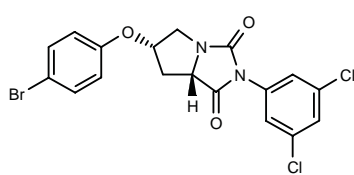
1. Beight, D.W. et al. (Eli Lilly and Company) *Novel sPLA₂ inhibitors*. WO 0250034.

TREATMENT OF MUSCULOSKELETAL AND CONNECTIVE TISSUE DISEASES

ANTIARTHRITIC DRUGS

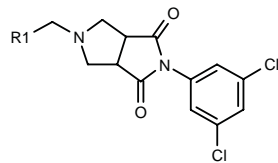
322388

(6*S*,7*aS*)-6-(4-Bromophenoxy)-2-(3,5-dichlorophenyl)perhydropyrrolo[1,2-*c*]imidazole-1,3-dione

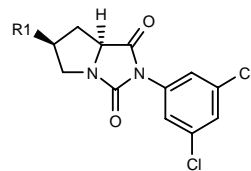


C18 H13 Br Cl2 N2 O3; Mol wt: 456.1217

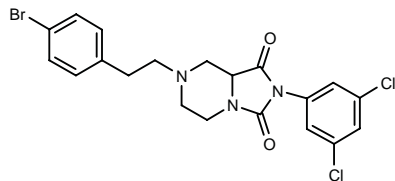
ACTION – Agent with the ability to inhibit cell adhesion by antagonizing the interaction between ICAM (intracellular adhesion molecule) molecules and leukointegrins (also known as the CD11/CD18 family of integrins), potentially useful for the treatment of inflammatory and immune disorders. Other exemplified compounds are:



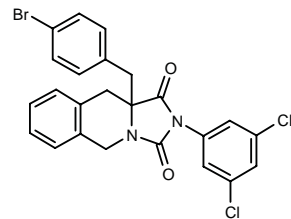
Compound	R1	Formula
322390	4-Cl-PhCH2	C ₂₀ H ₁₇ Cl ₃ N ₂ O ₂
322395	4-Br-PhCO	C ₂₀ H ₁₅ BrCl ₂ N ₂ O ₃
322396	2-Naph	C ₂₃ H ₁₈ Cl ₂ N ₂ O ₂



Compound	R1	Formula
322392	4-CN-PhCH2NH	C ₂₀ H ₁₆ Cl ₂ N ₄ O ₂
322393	4-CN-PhCH2N(Ac)	C ₂₂ H ₁₈ Cl ₂ N ₄ O ₃
322397	4-Br-PhCOO	C ₁₉ H ₁₃ BrCl ₂ N ₂ O ₄



322391: C20 H18 Br Cl2 N3 O2



322398: C24 H17 Br Cl2 N2 O2

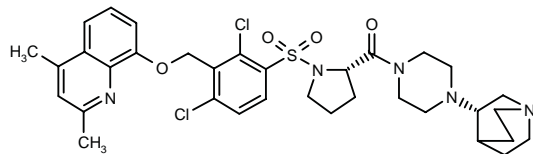
SOURCES – Bristol-Myers Squibb; Cerep.

REFERENCES

1. Iwanowicz, E.J. et al. (Bristol-Myers Squibb Co.;Cerep SA) *Hydantoin cpds. useful as anti-inflammatory agents*. WO 0244181.

322557

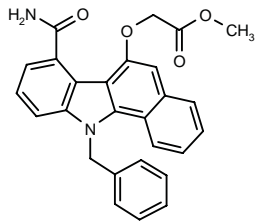
1-[4-[1-Azabicyclo[2.2.2]oct-3(*S*)-yl]piperazin-1-yl]-1-[1-[2,4-dichloro-3-(2,4-dimethylquinolin-8-yloxymethyl)-phenylsulfonyl]pyrrolidin-2(*S*)-yl]methanone



C34 H41 Cl2 N5 O4 S; Mol wt: 686.7009

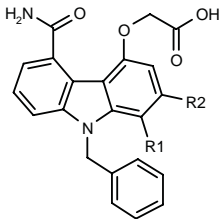
323470

2-(11-Benzyl-7-carbamoyl-11 *H*-benzo[*a*]carbazol-6-yloxy)acetic acid methyl ester



C27 H22 N2 O4; Mol wt: 438.4808

ACTION – Secretory phospholipase A₂ (sPLA₂) inhibitor (IC₅₀ = 38.6 μM), expected to be useful for the treatment of inflammatory disorders such as septic shock, inflammatory bowel disease, adult respiratory distress syndrome, pancreatitis, trauma, asthma, allergic rhinitis, rheumatoid arthritis, osteoarthritis, etc. Other exemplified compounds are:



Compound	R1	R2	Formula
323471		-(CH2)4-	C ₂₆ H ₂₄ N ₂ O ₄
323472		-(CH2)3-	C ₂₅ H ₂₂ N ₂ O ₄

SOURCE – Lilly.

REFERENCES

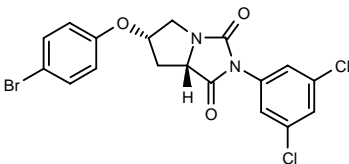
1. Beight, D.W. et al. (Eli Lilly and Company) *Novel sPLA₂ inhibitors*. WO 0250034.

TREATMENT OF MUSCULOSKELETAL AND CONNECTIVE TISSUE DISEASES

ANTIARTHRITIC DRUGS

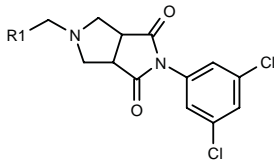
322388

(6*S*,7*aS*)-6-(4-Bromophenoxy)-2-(3,5-dichlorophenyl)perhydropyrrolo[1,2-*c*]imidazole-1,3-dione

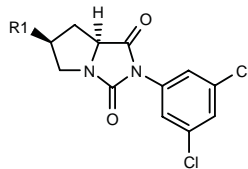


C18 H13 Br Cl2 N2 O3; Mol wt: 456.1217

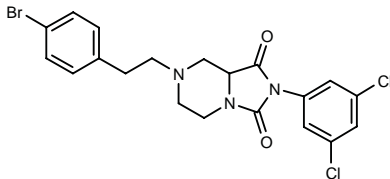
ACTION – Agent with the ability to inhibit cell adhesion by antagonizing the interaction between ICAM (intracellular adhesion molecule) molecules and leukointegrins (also known as the CD11/CD18 family of integrins), potentially useful for the treatment of inflammatory and immune disorders. Other exemplified compounds are:



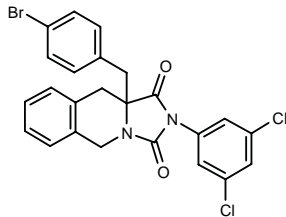
Compound	R1	Formula
322390	4-Cl-PhCH2	C ₂₀ H ₁₇ Cl ₃ N ₂ O ₂
322395	4-Br-PhCO	C ₂₀ H ₁₅ BrCl ₂ N ₂ O ₃
322396	2-Naph	C ₂₃ H ₁₈ Cl ₂ N ₂ O ₂



Compound	R1	Formula
322392	4-CN-PhCH2NH	C ₂₀ H ₁₆ Cl ₂ N ₄ O ₂
322393	4-CN-PhCH2N(Ac)	C ₂₂ H ₁₈ Cl ₂ N ₄ O ₃
322397	4-Br-PhCOO	C ₁₉ H ₁₃ BrCl ₂ N ₂ O ₄



322391: C20 H18 Br Cl2 N3 O2



322398: C24 H17 Br Cl2 N2 O2

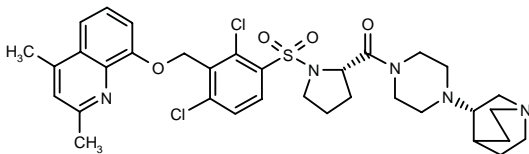
SOURCES – Bristol-Myers Squibb; Cerep.

REFERENCES

1. Iwanowicz, E.J. et al. (Bristol-Myers Squibb Co.;Cerep SA) *Hydantoin cpds. useful as anti-inflammatory agents*. WO 0244181.

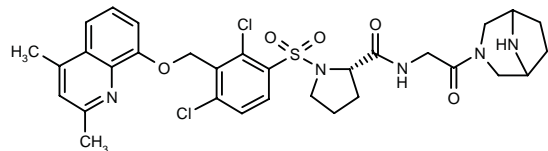
322557

1-[4-[1-Azabicyclo[2.2.2]oct-3(*S*)-yl]piperazin-1-yl]-1-[1-[2,4-dichloro-3-(2,4-dimethylquinolin-8-yloxymethyl)-phenylsulfonyl]pyrrolidin-2(*S*)-yl]methanone



C34 H41 Cl2 N5 O4 S; Mol wt: 686.7009

ACTION – Bradykinin receptor antagonist with potential use for the treatment of inflammation, rheumatoid arthritis, cystitis, posttraumatic or postischemic cerebral edema, liver cirrhosis, Alzheimer's disease, cardiovascular disease, pain, the common cold, allergies, asthma, pancreatitis, burns, viral infections, head injury, multiple trauma, rhinitis, hepatorenal failure, diabetes, metastasis, angiogenesis, corneal haze, glaucoma, ocular pain and ocular hypertension, among other bradykinin-mediated disorders. Another specifically claimed proline derivative is:



322558: C31 H35 Cl2 N5 O5 S

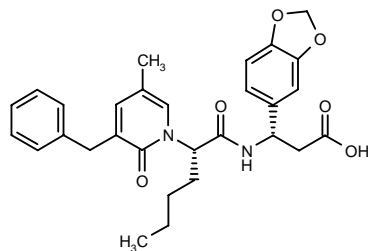
SOURCE – Pfizer.

REFERENCES

1. Katsu, Y. et al. (Pfizer Inc.) *N*-Benzenesulfonyl L-proline cpds. as bradykinin antagonists. EP 1213289.

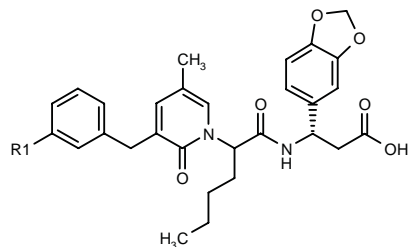
322561

3(*S*)-(1,3-Benzodioxol-5-yl)-3-[2(*S*)-(3-benzyl-5-methyl-2-oxo-1,2-dihydropyridin-1-yl)hexanamido]propionic acid



C29 H32 N2 O6; Mol wt: 504.5798

ACTION – Inhibitor of $\alpha_4\beta_1$ (VLA-4) integrin binding to VCAM-1 and fibronectin, proven to inhibit $\alpha_4\beta_1$ -mediated cell adhesion with an IC_{50} of 3 nM. Potentially useful for the treatment of atherosclerosis, rheumatoid arthritis, asthma, allergy, multiple sclerosis, lupus, inflammatory bowel disease, transplant rejection, contact hypersensitivity, type 1 diabetes and cancer. Other exemplified compounds are:



Compound	R1	Formula
322562	H	C ₂₉ H ₃₂ N ₂ O ₆
322563	Cl	C ₂₉ H ₃₁ ClN ₂ O ₆

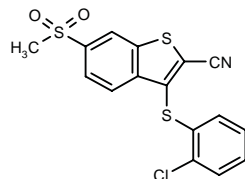
SOURCE – Texas Biotechnology.

REFERENCES

1. Biediger, R.J. et al. (Texas Biotechnology Corp.) *Propanoic acid derivs. that inhibit the binding of integrins to their receptors*. EP 1213288.

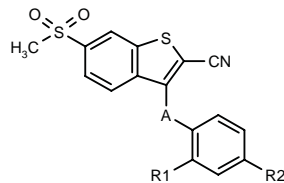
322751

3-(2-Chlorophenylsulfonyl)-6-(methylsulfonyl)benzo[*b*]-thiophene-2-carbonitrile



C16 H10 Cl N O2 S3; Mol wt: 379.9110

ACTION – Cyclooxygenase (COX) inhibitor that displayed an IC_{50} of < 1.0 μ M against COX-2 and exhibited > 120-fold selectivity over COX-1 *in vitro*. Potentially useful for the treatment of inflammatory disorders such as myositis, synovitis, arthritis, gout, back pain, dental pain, sports injuries, sprains, strains, headache, tendonitis, ankylosing spondylitis and bursitis, as well as for the treatment of dysmenorrhea, preterm labor and Alzheimer's disease. Other specifically claimed compounds are:



Compound	R1	R2	A	Formula
322754	Cl	Cl	S	C ₁₆ H ₉ Cl ₂ NO ₂ S ₃
322756	H	OE <i>t</i>	O	C ₁₈ H ₁₅ NO ₄ S ₂
322757	F	H	S	C ₁₆ H ₁₀ FNO ₂ S ₃
322758	H	F	S	C ₁₆ H ₁₀ FNO ₂ S ₃
322760	F	Cl	O	C ₁₆ H ₉ ClFNO ₃ S ₂

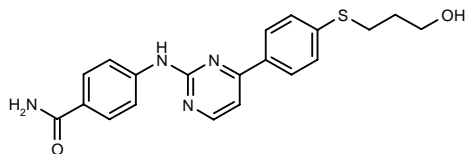
SOURCE – Roche.

REFERENCES

1. Mc Laren, K.L. et al. (F. Hoffmann-La Roche AG) *Benzofuran and benzothiophene derivs*. US 6433005, WO 0246178.

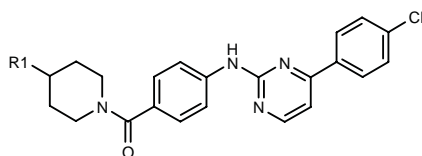
322782

4-[4-[4-(3-Hydroxypropylsulfonyl)phenyl]pyrimidin-2-ylamino]benzamide



C20 H20 N4 O2 S; Mol wt: 380.4700

ACTION – Inhibitor of the Jun *N*-terminal kinase (JNK) pathway and I κ B kinase IKK-2 that displayed IC₅₀ values of < 1 μ M against JNK2 and of < 500 nM against IKK-2. Claimed for use in the treatment of inflammatory and autoimmune diseases including arthritis, gout, asthma, bronchitis, allergic rhinitis, chronic obstructive pulmonary disease, Crohn's disease, psoriasis and multiple sclerosis, cardiovascular, metabolic and ischemic conditions, viral infections, cancer, stroke, epilepsy, Alzheimer's disease and Parkinson's disease. Other exemplified anilino-pyrimidine derivatives are:



Compound	R1	Formula
322783	OH	C ₂₂ H ₂₁ ClN ₄ O ₂
322784	NHAc	C ₂₄ H ₂₄ ClN ₅ O ₂
322785	NHCH ₂ CH ₂ OH	C ₂₄ H ₂₆ ClN ₅ O ₂

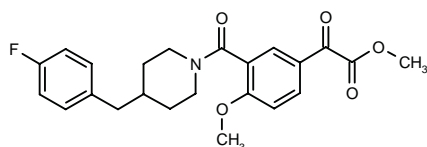
SOURCE – Signal (Celgene).

REFERENCES

1. Kois, A. et al. (Signal Pharmaceuticals, Inc.) *Anilinopyrimidine derivs. as IKK inhibitors and compns. and methods related thereto*. WO 0246171.
2. Kois, A. et al. (Signal Pharmaceuticals, Inc.) *Anilinopyrimidine derivs. as JNK pathway inhibitors and compns. and methods related thereto*. WO 0246170.

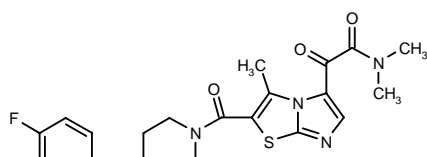
322825

2-[3-[4-(4-Fluorobenzyl)piperidin-1-ylcarbonyl]-4-methoxyphenyl]-2-oxoacetic acid methyl ester

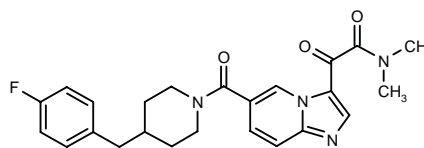


C23 H24 F N O5; Mol wt: 413.4426

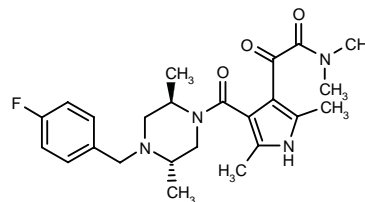
ACTION – An inhibitor of p38 α kinase with potential in the treatment of inflammatory disorders including multiple sclerosis, inflammatory bowel disease, arthritis, sepsis, septic shock, asthma, adult respiratory distress syndrome, stroke, reperfusion injury, CNS injury, psoriasis, restenosis, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcosis, bone resorption, transplant rejection, Crohn's disease, ulcerative colitis, Alzheimer's disease, pyresis and heart disease. Other exemplified piperazine and piperidine compounds are:



322826: C23 H25 F N4 O3 S



322827: C24 H25 F N4 O3



322828: C24 H31 F N4 O3

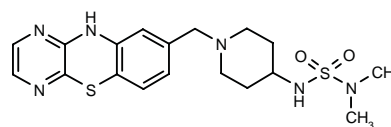
SOURCE – Scios.

REFERENCES

1. Dugar, S. et al. (Scios Inc.) *Piperidine/piperazine-type inhibitors of p38 kinase*. WO 0246158.

322839

N,N-Dimethyl-*N*'-[1-(10*H*-pyrazino[2,3-*b*][1,4]benzothiazin-8-ylmethyl)piperidin-4-yl]sulfamide



C18 H24 N6 O2 S2; Mol wt: 420.5596

ACTION – An inhibitor of intercellular adhesion molecule-1 (ICAM-1; IC₅₀ = 0.32 μ M) found to suppress the TNF- α -induced upregulation of E-selectin and VCAM-1 with respective IC₅₀ values of 0.55 and 0.36 μ M in human umbilical cord vascular endothelial cells. Compound exhibited good pharmacokinetics in rats with an oral bioavailability of 69%. In a model of IL-1-induced paw inflammation in mice, compound inhibited neutrophil infiltration in the paw at a dose of 10 mg/kg p.o. Potentially useful for the treatment of inflammatory diseases including rheumatoid arthritis, colitis, psoriasis and multiple sclerosis.

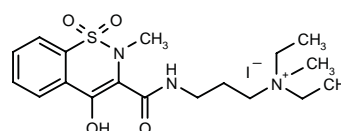
SOURCE – Eisai.

REFERENCES

1. Kaneko, T. et al. (Eisai Co., Ltd.) *Benzopiperidine derivs*. EP 0934941, WO 9806720.
2. Kaneko, T. et al. *Inhibitors of adhesion molecules expression: The synthesis and pharmacological properties of 10*H*-pyrazino[2,3-*b*][1,4]benzothiazine derivatives*. Chem Pharm Bull 2002, 50(7): 922.

323258

N,N-Diethyl-3-(4-hydroxy-2-methyl-1,1-dioxo-2*H*-1,2-benzothiazin-3-ylcarboxamido)-*N*-methylpropan-1-ammonium iodide



C18 H28 I N3 O4 S; Mol wt: 509.4022

ACTION – A representative compound from a series of 1,1-dioxo-1,2-benzothiazine-3-carboxamide derivatives with potential for the treatment of arthrosis and arthritis. Compound was shown to stimulate the production of aggrecan, a proteoglycan component of cartilage matrix, in IL-1-treated calf articular chondrocytes.

SOURCES – INSERM, Paris Cedex (FR); Servier.

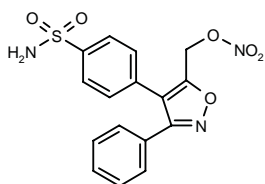
REFERENCES

1. Madelmont, J.-C. et al. (Servier Laboratoires; INSERM [Institut National de la Sante et de la Recherche Medicale]) *1,1-Dioxo-2H-1,2-benzothiazine-3-carboxamide derivs., method for preparing same and pharmaceutical compsns. comprising same*. FR 2818641, WO 0250049.

NMI-1093*

307614

4-[5-(Nitrooxymethyl)-3-phenylisoxazol-4-yl]benzene-sulfonamide



C16 H13 N3 O6 S; Mol wt: 375.3597

ACTION – Nitric-oxide (NO) enhanced cyclooxygenase type 2 (COX-2) selective inhibitor with IC_{50} values of 0.25 and $> 100 \mu M$ for inhibition of isolated COX-2 and COX-1, respectively, and IC_{50} values of 1.2 and $110 \mu M$ for inhibition of COX-2 and COX-1, respectively, in human whole blood. At doses of 1.4 and 2.8 mg/kg p.o., it exhibited comparable antiinflammatory efficacy to celecoxib in the carrageenan-induced paw edema in rats; it was also active in the air pouch model in rats, where doses of 5-15 mg/kg p.o. showed higher efficacy than rofecoxib and celecoxib. NMI-1093 inhibited ADP-induced platelet aggregation *in vitro* and showed antithrombotic activity in an arteriovenous shunt model in rats in a dose-dependent manner, producing a significant reduction of thrombus weight of 42% at 64 mg/kg p.o. Moreover, at 200 $\mu mol/kg$ p.o. it accelerated ulcer healing in a 7-day rat model of flurbiprofen-induced stomach irritation. Potentially useful as an antiarthritic and antithrombotic agent.

SOURCE – NitroMed.

REFERENCES

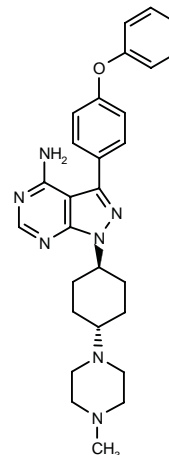
1. Bandarage, R.R. et al. (NitroMed Inc.) *Nitrosated and nitrosylated cyclooxygenase-2 inhibitors, compsns. and methods of use*. WO 0145703.
2. Janero, D.R. et al. *Novel nitrated cyclooxygenase-2 (COX-2) selective inhibitors are anti-thrombotic in vivo*. 14th World Congr Pharmacol (July 7-12, San Francisco) 2002, Abst LB 11.
3. Schroeder, J.D. et al. *NMI-1093: A nitric oxide-enhanced cyclooxygenase-2 selective inhibitor with cardioprotective potential*. 224th ACS Natl Meet (Aug 18-22, Boston) 2002, Abst MEDI 316.

*Identified compound **307614** Drug Data Rep 2001, 023(10): 1007.

IMMUNOMODULATING AGENTS

322887

trans-1-[4-(4-Methylpiperazin-1-yl)cyclohexyl]-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine



C28 H33 N7 O; Mol wt: 483.6167

ACTION – Immunosuppressant, a potent inhibitor of the nonreceptor tyrosine kinase Lck ($IC_{50} = 40 \text{ nM}$), also active against the closely related tyrosine kinase Src ($IC_{50} = 35 \text{ nM}$) and selective relative to the receptor tyrosine kinases KDR and Tie-2 ($IC_{50} = 5.32$ and $0.75 \mu M$, respectively). *In vivo*, compound strongly inhibited anti-CD3 MAb-stimulated IL-2 production in mice ($ED_{50} = 1.5 \text{ mg/kg p.o.}$) and exhibited favorable pharmacokinetics in rats, with an oral bioavailability of 69%. Potentially useful for the treatment of autoimmune and inflammatory diseases, as well as for organ transplant rejection.

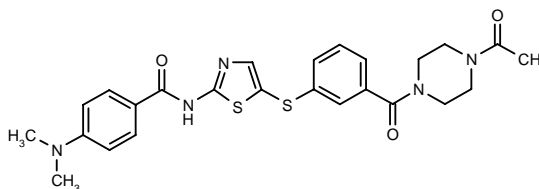
SOURCE – Abbott.

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2. Burchat, A.F. et al. *Pyrazolo[3,4-d]pyrimidines containing an extended 3-substituent as potent inhibitors of Lck - A selective insight*. Bioorg Med Chem Lett 2002, 12(12): 1687.

323444

N-[5-[3-(4-Acetylpiperazin-1-ylcarbonyl)phenylsulfanyl]-thiazol-2-yl]-4-(dimethylamino)benzamide



C25 H27 N5 O3 S2; Mol wt: 509.6523

ACTION – A representative compound from a series of 1,1-dioxo-1,2-benzothiazine-3-carboxamide derivatives with potential for the treatment of arthrosis and arthritis. Compound was shown to stimulate the production of aggrecan, a proteoglycan component of cartilage matrix, in IL-1-treated calf articular chondrocytes.

SOURCES – INSERM, Paris Cedex (FR); Servier.

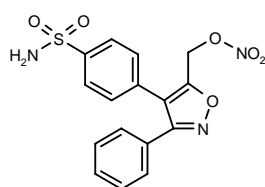
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NMI-1093*

307614

4-[5-(Nitrooxymethyl)-3-phenylisoxazol-4-yl]benzene-sulfonamide



C16 H13 N3 O6 S; Mol wt: 375.3597

ACTION – Nitric-oxide (NO) enhanced cyclooxygenase type 2 (COX-2) selective inhibitor with IC_{50} values of 0.25 and $> 100 \mu\text{M}$ for inhibition of isolated COX-2 and COX-1, respectively, and IC_{50} values of 1.2 and $110 \mu\text{M}$ for inhibition of COX-2 and COX-1, respectively, in human whole blood. At doses of 1.4 and 2.8 mg/kg p.o., it exhibited comparable antiinflammatory efficacy to celecoxib in the carrageenan-induced paw edema in rats; it was also active in the air pouch model in rats, where doses of 5-15 mg/kg p.o. showed higher efficacy than rofecoxib and celecoxib. NMI-1093 inhibited ADP-induced platelet aggregation *in vitro* and showed antithrombotic activity in an arteriovenous shunt model in rats in a dose-dependent manner, producing a significant reduction of thrombus weight of 42% at 64 mg/kg p.o. Moreover, at 200 $\mu\text{mol/kg}$ p.o. it accelerated ulcer healing in a 7-day rat model of flurbiprofen-induced stomach irritation. Potentially useful as an antiarthritic and antithrombotic agent.

SOURCE – NitroMed.

REFERENCES

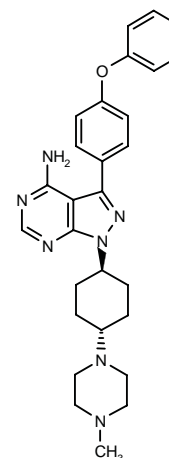
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2. Janero, D.R. et al. Novel nitrated cyclooxygenase-2 (COX-2) selective inhibitors are anti-thrombotic *in vivo*. 14th World Congr Pharmacol (July 7-12, San Francisco) 2002, Abst LB 11.
3. Schroeder, J.D. et al. NMI-1093: A nitric oxide-enhanced cyclooxygenase-2 selective inhibitor with cardioprotective potential. 224th ACS Natl Meet (Aug 18-22, Boston) 2002, Abst MEDI 316.

*Identified compound 307614 Drug Data Rep 2001, 023(10): 1007.

IMMUNOMODULATING AGENTS

322887

trans-1-[4-(4-Methylpiperazin-1-yl)cyclohexyl]-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine



C28 H33 N7 O; Mol wt: 483.6167

ACTION – Immunosuppressant, a potent inhibitor of the nonreceptor tyrosine kinase Lck ($IC_{50} = 40 \text{ nM}$), also active against the closely related tyrosine kinase Src ($IC_{50} = 35 \text{ nM}$) and selective relative to the receptor tyrosine kinases KDR and Tie-2 ($IC_{50} = 5.32$ and $0.75 \mu\text{M}$, respectively). *In vivo*, compound strongly inhibited anti-CD3 MAb-stimulated IL-2 production in mice ($ED_{50} = 1.5 \text{ mg/kg p.o.}$) and exhibited favorable pharmacokinetics in rats, with an oral bioavailability of 69%. Potentially useful for the treatment of autoimmune and inflammatory diseases, as well as for organ transplant rejection.

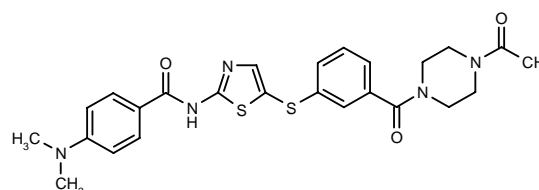
SOURCE – Abbott.

REFERENCES

1. Hirst, G.C. et al. (BASF AG) Pyrazolopyrimidines as therapeutic agents. EP 1212327, WO 0119829.
2. Burchat, A.F. et al. Pyrazolo[3,4-*d*]pyrimidines containing an extended 3-substituent as potent inhibitors of Lck - A selective insight. Bioorg Med Chem Lett 2002, 12(12): 1687.

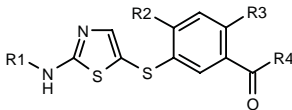
323444

N-[5-[3-(4-Acetylpiperazin-1-ylcarbonyl)phenylsulfanyl]-thiazol-2-yl]-4-(dimethylamino)benzamide

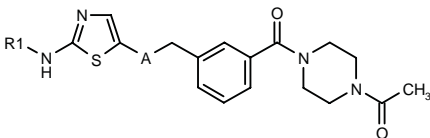


C25 H27 N5 O3 S2; Mol wt: 509.6523

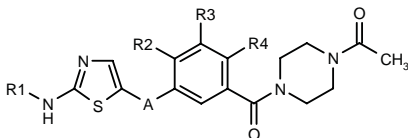
ACTION – Inhibitor of Tec tyrosine kinases, particularly ITK (IL-2-inducible T-cell kinase, or EMT). Potentially useful for the treatment of immune, inflammatory, allergic and proliferative disorders including transplant rejection, rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease, lupus, psoriasis, T-cell-mediated hypersensitivity, Hashimoto’s thyroiditis, Guillain-Barré syndrome, cancer, contact dermatitis, allergy, asthma, ischemia–reperfusion injury, atopic dermatitis, allergic rhinitis and chronic obstructive pulmonary disease. Other exemplified thiazole derivatives are:



Compound	R1	R2	R3	R4	Formula
323445	2-Pyr	H	Me	4-(2H-5-tetrazolyl)-1-Pip	C ₂₂ H ₂₂ N ₈ OS ₂
323451	cyclopropyl-CO	Me	OMe	4-(NH ₂ CH ₂ CO)-1-Piz	C ₂₂ H ₂₇ N ₅ O ₄ S ₂
323452	2-Pyr	H	Me	2-Cl-6-F-PhCH ₂ -SCH ₂ CH ₂ NH	C ₂₅ H ₂₂ ClF ₄ OS ₃



Compound	R1	A	Formula
323447	2-Pyr	-CH ₂ N(i-Pr)-	C ₂₆ H ₃₂ N ₆ O ₂ S
323449	4-[3(R)-(CH ₂ OH)bicyclo[2.2.1]-hept-2(S)-yl-NHCH ₂]-PhCO	-S-	C ₃₃ H ₃₉ N ₅ O ₄ S ₂



Compound	R1	R2	R3	R4	A	Formula
323450	2-pyrrolyl-CO	H	Me	Me	-SCH ₂ -	C ₂₄ H ₂₇ N ₅ O ₃ S ₂
323453	6-Br-2-Pyr	H	H	Me	-O-	C ₂₂ H ₂₂ BrN ₅ O ₃ S
323454	2-Me-6-(4-morpholinyl-CH ₂ CH ₂ NH)-4-pyrimidinyl	Me	H	OMe	-S-	C ₂₉ H ₃₈ N ₈ O ₄ S ₂

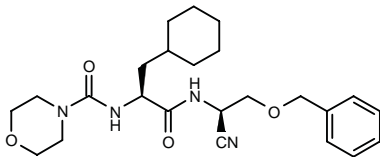
SOURCE – Bristol-Myers Squibb.

REFERENCES

1. Barrish, J.C. et al. (Bristol-Myers Squibb Co.) *Thiazolyl inhibitors of Tec family tyrosine kinases*. WO 0250071.

323758

N-[1(*S*)-[*N*-2-(Benzyloxy)-1(*R*)-cyanoethyl]carbamoyl]-2-cyclohexylethyl]morpholine-4-carboxamide



C24 H34 N4 O4; Mol wt: 442.5566

ACTION– Potent and reversible cathepsin S inhibitor with *in vitro* activity in the nanomolar range and cellular activity in human B-cells. Potentially useful as an immuno-modulator.

SOURCE – Boehringer Ingelheim.

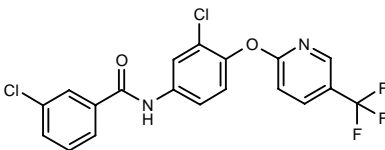
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1. Cywin, C.L. et al. (Boehringer Ingelheim Pharmaceuticals Inc.) *Cpds. useful as reversible inhibitors of cathepsin S*. US 6395897, WO 0051998.

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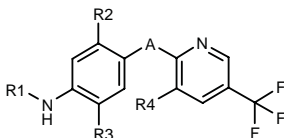
323870

3-Chloro-*N*-[3-chloro-4-[5-(trifluoromethyl)pyridin-2-yloxy]phenyl]benzamide

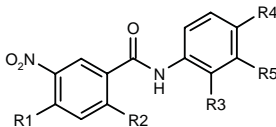


C19 H11 Cl2 F3 N2 O2; Mol wt: 427.2079

ACTION – Agent with the ability to inhibit the production of Th1- and/or Th2-type cytokines, proven to completely inhibit the production of IL-5 (Th2 cytokine) and interferon (Th1 cytokine) in anti-murine CD3 antibody-challenged mouse spleen cells at 100 ppm. Potentially useful for the treatment of allergic diseases such as urticaria, food allergy, asthma, allergic rhinitis, allergic conjunctivitis and atopic dermatitis, and autoimmune diseases including systemic lupus erythematosus, rheumatoid arthritis, type 1 diabetes, Hashimoto’s thyroiditis, myasthenia gravis, multiple sclerosis and transplant rejection. Other exemplified anilide derivatives are:



Compound	R1	R2	R3	R4	A	Formula
323871	2-OH-PhCO	Cl	H	H	O	C ₁₉ H ₁₂ ClF ₃ N ₂ O ₃
323875	2-Cl-5-NO ₂ -PhSO ₂	H	H	Cl	O	C ₁₈ H ₁₀ Cl ₂ F ₃ N ₃ O ₅ S
323876	2-Cl-5-NO ₂ -PhSO ₂	H	H	Cl	S	C ₁₈ H ₁₀ Cl ₂ F ₃ N ₃ O ₄ S ₂
323878	2-Cl-5-NO ₂ -PhCO	H	CO ₂ Me	Cl	O	C ₂₁ H ₁₂ Cl ₂ F ₃ N ₃ O ₆



Compound	R1	R2	R3	R4	R5	Formula
323872	H	H	Me	1-adamantyl	H	C ₂₄ H ₂₆ N ₂ O ₃
323873	H	Cl	H	H	OPh	C ₁₉ H ₁₃ ClN ₂ O ₄
323874	Cl	H	Me	1-adamantyl	H	C ₂₄ H ₂₅ ClN ₂ O ₃
323879	H	Cl	H	-N=CHS-		C ₁₄ H ₈ ClN ₃ O ₃ S

SOURCE – Ishihara Sangyo.

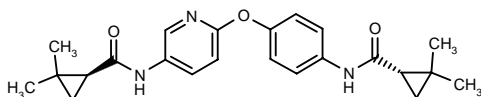
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APC-0576*

299820

N-[6-[4-[(1*S*)-2,2-Dimethylcyclopropylcarboxamido]-phenoxy]pyridin-3-yl]-2,2-dimethylcyclopropane-1(*S*)-carboxamide



C23 H27 N3 O3; Mol wt: 393.4843

ACTION – Immunosuppressant, a small-molecule inhibitor of NF-κB-dependent gene activation, able to inhibit IL-1-induced NF-κB-dependent transcriptional activation in endothelial NF-κB reporter cells. It inhibited NF-κB-dependent β-galactosidase (β-gal) activity ($IC_{50} = 1.0 \mu M$), while having little or no effect on cell viability at much higher concentrations. It also inhibited β-galactosidase activity induced by other types of stimulation such as TNF, lipopolysaccharide (LPS) and PMA, with similar IC_{50} values. In both endothelial cells and primary human umbilical vein endothelial cells (HUVEC), compound inhibited IL-1-induced IL-8 and MCP-1 release. The effects of the drug were found to occur at the level of mRNA expression. In monkeys, 4 weeks of treatment with 10-50 mg/kg b.i.d. p.o. dose-dependently suppressed both the delayed-type hypersensitivity reaction and specific antibody formation induced by tetanus toxoid injection. Moreover, the compound protected monkeys from kidney transplant rejection during 4 weeks of treatment at a dose of 50 mg/kg b.i.d. p.o. Potentially useful for the treatment of diseases involving endothelial activation including allograft rejection, rheumatoid arthritis, asthma, inflammatory bowel disease, cardiovascular disorders and diabetic microangiopathy.

SOURCE – Ajinomoto.

REFERENCES

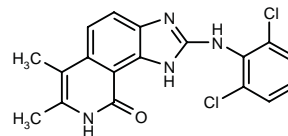
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2. Takehana, K. et al. *APC0576, a novel inhibitor of NF-κB-dependent gene activation, prevents pro-inflammatory cytokine-induced chemokine production in human endothelial cells*. Biochem Biophys Res Commun 2002, 293(3): 945.
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*Identified compound **299820** Drug Data Rep 2001, 023(06): 0587.

BIRA-0596

316278

2-(2,6-Dichlorophenylamino)-6,7-dimethyl-8,9-dihydro-1*H*-imidazo[4,5-*h*]isoquinolin-9-one



C18 H14 Cl2 N4 O; Mol wt: 373.2416

ACTION – Potent and selective lck tyrosine kinase inhibitor ($IC_{50} = 0.026 \mu M$) with comparable potency for c-Src tyrosine kinase ($IC_{50} = 0.012 \mu M$) and high selectivity over other kinases including the receptor tyrosine kinase EGFR (epidermal growth factor receptor), the nonreceptor tyrosine kinases Zap70 and Syk, and the serine/threonine kinases p38 and Erk. In a cellular assay using Jurkat cells, compound inhibited anti-CD3 MAb-induced calcium mobilization ($EC_{50} = 0.19 \mu M$) and IL-2 production ($EC_{50} = 1 \mu M$). In mice, it significantly inhibited anti-CD3 MAb-induced IL-2 production at a dose of 100 mg/kg i.p. but was inactive after oral administration. Potential immunosuppressant for the treatment of autoimmune diseases.

SOURCE – Boehringer Ingelheim.

REFERENCES

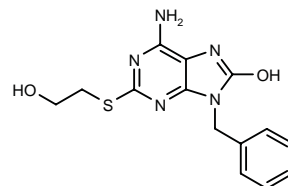
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3. Snow, R.J. et al. *The discovery of 2-phenylamino-imidazo[4,5-h]isoquinolin-9-ones, a new class of inhibitors of lck kinase with in vivo activity*. Cell Mol Biol Lett 2001, 6(2B): 524.

SM-295072*

279090

6-Amino-9-benzyl-2-(2-hydroxyethylsulfanyl)-9*H*-purin-8-ol

9-Benzyl-8-hydroxy-2-(2-hydroxyethylsulfanyl)adenine



C14 H15 N5 O2 S; Mol wt: 317.3715

ACTION – Interferon inducer able to enhance the release of interferon *in vitro* in mouse spleen cells ($MIC = 0.1 \mu M$) and *in vivo* in mice ($MED = 0.1 \text{ mg/kg p.o.}$). Compound also showed antitumor activity in mice. Potentially useful as an immunostimulant.

SOURCES – Japan Energy; Sumitomo Pharmaceuticals.

REFERENCES

1. Kurimoto, A. et al. (Sumitomo Pharmaceuticals Co., Ltd.;Japan Energy Corp.) *Novel heterocyclic cpds.* EP 1035123, US 6329381, WO 9928321.

2. Kurimoto, A. et al. *Synthesis and structure-activity relationships of 8-hydroxy-adenines as interferon inducers.* 224th ACS Natl Meet (Aug 18-22, Boston) 2002, Abst MEDI 41.

3. Ogino, T. et al. *Synthesis of 8-hydroxyadenine derivatives possessing IFN inducing activity - Study to optimize the 2-position of the adenine ring (I).* 21st Symp Med Chem (Nov 28-30, Kyoto) 2001, Abst 1P-10.

*Identified compound **279090** Drug Data Rep 1999, 021(10): 0922.

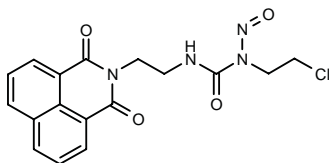
ONCOLYTIC DRUGS

DNA-DAMAGING DRUGS

NAPHTHAL-NU

322936

N-(2-Chloroethyl)-*N'*-[2-(1,3-dioxo-2,3-dihydro-1*H*-benzo[*de*]isoquinolin-2-yl)ethyl]-*N*-nitrosourea



C17 H15 Cl N4 O4; Mol wt: 374.7825

ACTION – Antineoplastic agent with DNA-alkylating activity greater than that of lomustine, and *in vivo* anti-tumor activity in mice bearing sarcoma 180 and Ehrlich ascites carcinoma. In these models, compound significantly inhibited tumor growth and increased life span; the maximal effect was achieved at the dose of 50 mg/kg s.c., at which a therapeutic index of 235 was found.

SOURCE – Chittaranjan National Cancer Institute, Calcutta (IN).

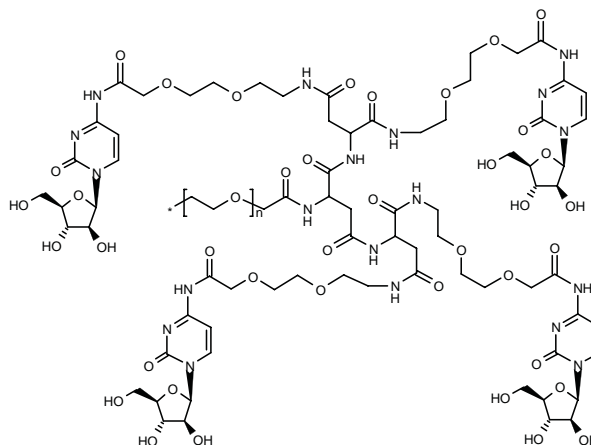
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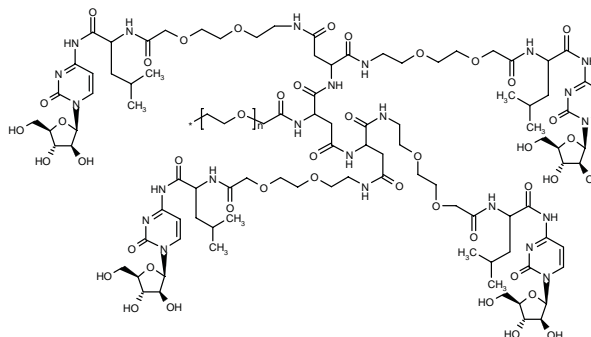
ANTIMETABOLITES

320802

1-β-D-Arabinofuranosyl-*N*⁴-[2-[2-[2-[4-[2-[2-[2-(1-β-D-arabinofuranosylcytosin-*N*⁴-yl)-2-oxoethoxy]ethoxy]-ethylamino]-2-[4-[1,2-bis[*N*-[2-[2-[2-[1-β-D-arabinofuranosylcytosin-*N*⁴-yl]-2-oxoethoxy]ethoxy]ethyl]carbamoyl]ethylamino]-3-[2-(polyethylene glycol)acetamido]-succinamido]succinamido]ethoxy]ethoxy]acetyl]cytosine



ACTION – Polyethylene glycol (PEG)-multiloaded ara C prodrug with improved water solubility and antitumor activity compared to the parent drug. The prodrug is stable in PBS but was rapidly hydrolyzed in rat and human plasma. The *in vitro* cytotoxicity of prodrug was not increased in comparison with the parent drug (IC₅₀ = 39 and 10 nM against murine leukemia P388/O cells), whereas *in vivo* it exhibited stronger antineoplastic activity than ara C in various cancer models. In mice bearing orthotopic pancreatic ductal adenocarcinoma (PANC-1) xenografts, the prodrug (40 or 60 mg/kg i.v.) showed significantly better tumor growth inhibition than ara C (100 mg/kg i.v.); in mice with murine ascitic leukemia, a dose of 60 mg/kg i.v. increased life span and produced cure in 70% of animals. Another related compound is:



320804

SOURCES – Japan Energy; Sumitomo Pharmaceuticals.

REFERENCES

1. Kurimoto, A. et al. (Sumitomo Pharmaceuticals Co., Ltd.;Japan Energy Corp.) *Novel heterocyclic cpds.* EP 1035123, US 6329381, WO 9928321.

2. Kurimoto, A. et al. *Synthesis and structure-activity relationships of 8-hydroxy-adenines as interferon inducers.* 224th ACS Natl Meet (Aug 18-22, Boston) 2002, Abst MEDI 41.

3. Ogino, T. et al. *Synthesis of 8-hydroxyadenine derivatives possessing IFN inducing activity - Study to optimize the 2-position of the adenine ring (I).* 21st Symp Med Chem (Nov 28-30, Kyoto) 2001, Abst 1P-10.

*Identified compound **279090** Drug Data Rep 1999, 021(10): 0922.

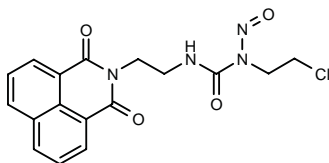
ONCOLYTIC DRUGS

DNA-DAMAGING DRUGS

NAPHTHAL-NU

322936

N-(2-Chloroethyl)-*N'*-[2-(1,3-dioxo-2,3-dihydro-1*H*-benzo[*de*]isoquinolin-2-yl)ethyl]-*N*-nitrosourea



C17 H15 Cl N4 O4; Mol wt: 374.7825

ACTION – Antineoplastic agent with DNA-alkylating activity greater than that of lomustine, and *in vivo* anti-tumor activity in mice bearing sarcoma 180 and Ehrlich ascites carcinoma. In these models, compound significantly inhibited tumor growth and increased life span; the maximal effect was achieved at the dose of 50 mg/kg s.c., at which a therapeutic index of 235 was found.

SOURCE – Chittaranjan National Cancer Institute, Calcutta (IN).

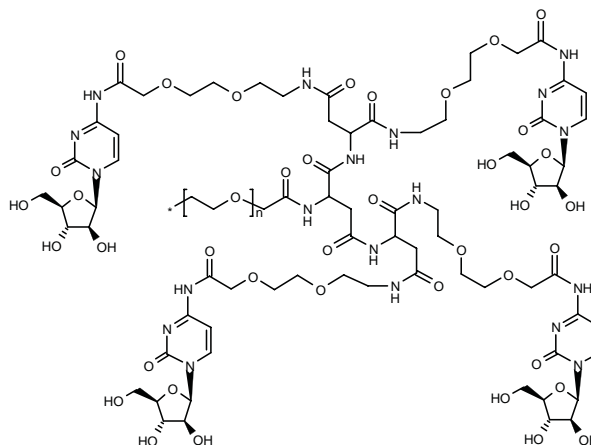
REFERENCES

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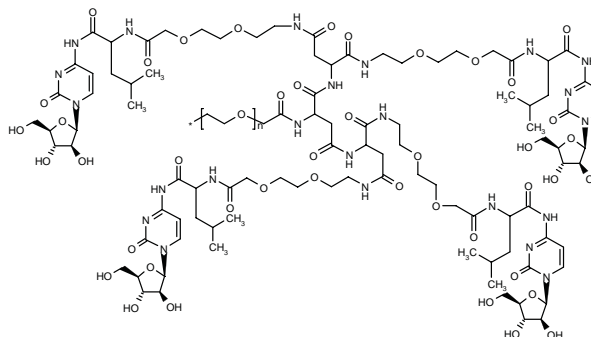
ANTIMETABOLITES

320802

1-β-D-Arabinofuranosyl-*N*⁴-[2-[2-[2-[4-[2-[2-[2-(1-β-D-arabinofuranosylcytosin-*N*⁴-yl)-2-oxoethoxy]ethoxy]-ethylamino]-2-[4-[1,2-bis[*N*-[2-[2-[2-[1-β-D-arabinofuranosylcytosin-*N*⁴-yl]-2-oxoethoxy]ethoxy]ethyl]carbamoyl]ethylamino]-3-[2-(polyethylene glycol)acetamido]-succinamido]succinamido]ethoxy]ethoxy]acetyl]cytosine



ACTION – Polyethylene glycol (PEG)-multiloaded ara C prodrug with improved water solubility and antitumor activity compared to the parent drug. The prodrug is stable in PBS but was rapidly hydrolyzed in rat and human plasma. The *in vitro* cytotoxicity of prodrug was not increased in comparison with the parent drug (IC₅₀ = 39 and 10 nM against murine leukemia P388/O cells), whereas *in vivo* it exhibited stronger antineoplastic activity than ara C in various cancer models. In mice bearing orthotopic pancreatic ductal adenocarcinoma (PANC-1) xenografts, the prodrug (40 or 60 mg/kg i.v.) showed significantly better tumor growth inhibition than ara C (100 mg/kg i.v.); in mice with murine ascitic leukemia, a dose of 60 mg/kg i.v. increased life span and produced cure in 70% of animals. Another related compound is:



320804

SOURCE – Enzon.

REFERENCES

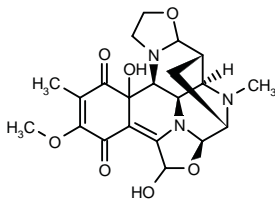
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ANTIBIOTICS AND ALKALOIDS

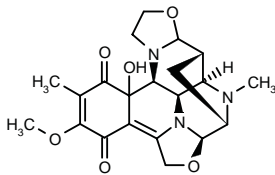
322454

(6a*R*,7*S*,8a*R*,8b*R*,9*S*,12b*S*)-5,12c-Dihydroxy-3-methoxy-2,8-dimethyl-1,4,5,6a,7,8,8a,8b,9,9a,11,12,12b,12c-tetradecahydro-7,9-methano-6,10-dioxo-8,8c,12a-triazaindeno[6,5,4-*fg*]aceanthrylene-1,4-dione



C21 H25 N3 O7; Mol wt: 431.4425

ACTION – Antitumor polycyclic compound isolated from cultures of *Streptomyces halstedii* KB012 (FERM P-18062). This compound was shown to inhibit the growth of *Bacillus subtilis* strains M45T (*rec*⁻ mutant) and HA17 (*rec*⁺ parent strain). It also inhibited the proliferation of human leukemia K562 cells with an IC₅₀ of 2.12 µg/ml. Another compound from the same source is:



322455: C21 H25 N3 O6

SOURCE – Mercian.

REFERENCES

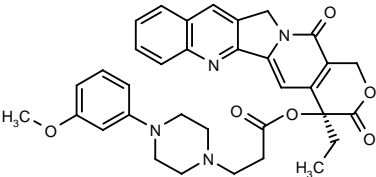
1. Yoshimoto, A. et al. (Mercian Corp.) *Novel benzoquinone antibiotics.* JP 2002155087.

DNA-INTERCALATING DRUGS

322729

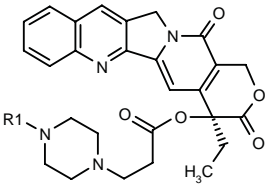
3-[4-(3-Methoxyphenyl)piperazin-1-yl]propionic acid 4(*S*)-ethyl-3,14-dioxo-3,4,12,14-tetrahydro-1*H*-pyrano-[3',4':6,7]indolizino[1,2-*b*]quinolin-4-yl ester

20(*S*)-*O*-[3-[4-(3-Methoxyphenyl)piperazin-1-yl]-propionyl]camptothecin

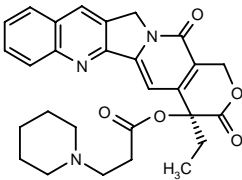


C34 H34 N4 O6; Mol wt: 594.6646

ACTION – Camptothecin derivative with potential as an antitumor agent with low toxicity. Compound was able to completely prevent the proliferation of human colon carcinoma HCT 116 cells at 10 nM. In acute toxicity tests in mice, it exhibited a maximum tolerated dose (MTD) of 150 mg/kg i.p. Other exemplified compounds are:



Compound	R1	Formula
322730	3-CF3-Ph	C ₃₄ H ₃₁ F ₃ N ₄ O ₅
322731	CH2Ph	C ₃₄ H ₃₄ N ₄ O ₅
322733	4-NO2-Ph	C ₃₃ H ₃₁ N ₅ O ₇



322732: C28 H29 N3 O5

SOURCE – California Pacific Medical Center Institute, San Francisco, CA (US).

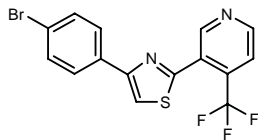
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1. Yang, L.-X. et al. (California Pacific Medical Center Institute) *Nitrogen-based camptothecin derivs.* US 6403604.

HORMONAL AGENTS

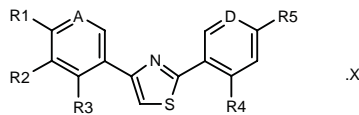
322878

3-[4-(4-Bromophenyl)thiazol-2-yl]-4-(trifluoromethyl)-pyridine



C15 H8 Br F3 N2 S; Mol wt: 385.2062

ACTION – Inhibitor of steroid 17- α -hydroxylase/17,20 lyase (steroid 17- α -monooxygenase; IC₅₀ < 10 nM). Potentially useful for the treatment of androgen- and estrogen-dependent cancer and other disorders such as prostatic hypertrophy, virilism, hypertrichosis, male pattern baldness, male prematurity, endometriosis, uterine leiomyoma, uterine adenomyosis, mastopathy and polycystic ovary syndrome. Other exemplified substituted thiazole derivatives are:



Compound	R1	R2	R3	R4	R5	A	D	X	Formula
322880	H	OMe	H	H	H	CH	N	HBr	C ₁₅ H ₁₂ N ₂ OS.HBr
322881	OMe	H	H	CF ₃	H	CH	N	HCl	C ₁₆ H ₁₁ F ₃ N ₂ OS.HCl
322882	F	H	H	Me	H	CH	N		C ₁₅ H ₁₁ FN ₂ S
322883	Me	H	Me	OMe	H	CH	N	HCl	C ₁₇ H ₁₆ N ₂ OS.HCl
322884	Me	H	H	Me	H	CH	N		C ₁₆ H ₁₄ N ₂ S
322885	H	H	H	H	F	N	CH	HBr	C ₁₄ H ₉ FN ₂ S.HBr

SOURCE – Takeda.

REFERENCES

1. Kusaka, M. et al. (Takeda Chemical Industries, Ltd.) *Substd. thiazole derivs. bearing 3-pyridyl groups, process for preparing the same and use thereof.* WO 0246186.

CANCER IMMUNOTHERAPY

MAb 2.13.2

324256

Monoclonal antibody that specifically binds to insulin-like growth factor I receptor (IGF-IR)

ACTION – Monoclonal antibody that specifically binds to insulin-like growth factor I receptor (IGF-IR). It demonstrated high affinity for the extracellular domain of IGF-IR and inhibited the IGF-I-mediated activation of IGF-IR (IC₅₀ = 0.0812 mg/ml). The antibody also inhibited the binding of [¹²⁵I]-IGF-I to cells overexpressing IGF-IR with an IC₅₀ value of 0.18 μ g/ml. Combination studies with the 2.13.2 antibody and doxorubicin in several animal models of cancer demonstrated an enhanced tumor growth delay versus treatment with the antibody or doxorubicin alone. MAb 2.13.2, alone or in combination with other antitumor agents, is potentially useful for the treatment of cancer.

SOURCES – Abgenix; Pfizer.

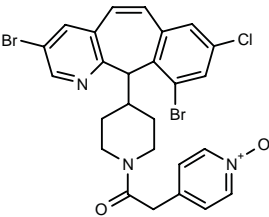
REFERENCES

1. Cohen, B.D. et al. (Pfizer Inc.;Abgenix, Inc.) *Antibodies to insulin-like growth factor I receptor.* WO 0253596.

INHIBITORS OF SIGNAL TRANSDUCTION PATHWAYS

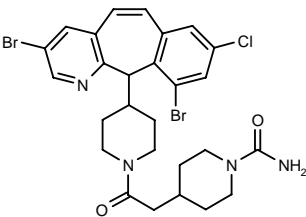
322272

1-[4-(3,10-Dibromo-8-chloro-11 *H*-benzo[5,6]cyclohepta-[1,2-*b*]pyridin-11-yl)piperidin-1-yl]-2-(1-oxidopyridin-4-yl)-ethanone



C26 H22 Br2 Cl N3 O2; Mol wt: 603.7398

ACTION – Protein farnesyltransferase (FTase) inhibitor (IC₅₀ = 0.32 nM) shown to inhibit the anchorage-independent growth of human tumor cells in soft agar with an IC₅₀ of 0.03 μ M. Potentially useful for the treatment of cancer. Another exemplified compound is:



322273: C27 H29 Br2 Cl N4 O2

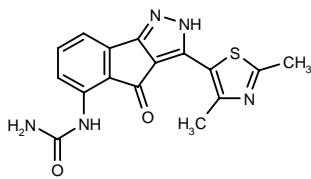
SOURCE – Schering-Plough.

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1. Njoroge, F.G. et al. (Schering Corp.) *Novel farnesyl protein transferase inhibitors*. WO 0244164.

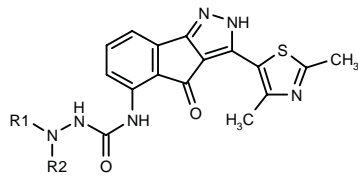
322288

N-[3-(2,4-Dimethylthiazol-5-yl)-4-oxo-2,4-dihydroindeno-[1,2-*c*]pyrazol-5-yl]urea



C16 H13 N5 O2 S; Mol wt: 339.3777

ACTION – Cyclin-dependent kinase (CDK) inhibitor, potentially useful for the treatment of cancer and other proliferative diseases including Alzheimer’s disease, viral and fungal infections, autoimmune diseases, psoriasis, vascular smooth cell proliferation associated with atherosclerosis, pulmonary fibrosis, arthritis, glomerulonephritis, neurodegenerative diseases and restenosis. Other specifically claimed compounds are:



Compound	R1	R2	Formula
322289	-CH2CH2OCH2CH2-		C20H20N6O3S
322290	Me	Ph	C23H20N6O2S
322291	-CH(Me)(CH2)3CH(Me)-		C23H26N6O2S
322292	-CH2CH2N(Me)CH2CH2-		C21H23N7O2S

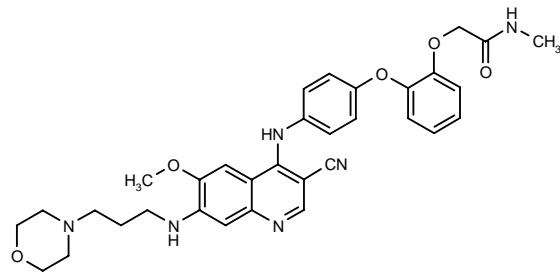
SOURCE – Bristol-Myers Squibb.

REFERENCES

1. Yue, E.W. (Bristol-Myers Squibb Co.) *3-(2,4-Dimethylthiazol-5-yl)indeno[1,2-c]pyrazol-4-one derivs. and their use*. WO 0244174.

322324

2-[2-[4-[3-Cyano-6-methoxy-7-[3-(4-morpholinyl)propyl-amino]quinolin-4-ylamino]phenoxy]phenoxy]-*N*-methylacetamide



C33 H36 N6 O5; Mol wt: 596.6844

ACTION – A representative compound from a series of quinoline derivatives that act as inhibitors of mitogen ERK kinase (MEK) and may therefore be useful as antitumor agents. This compound inhibited MEK-induced MAP kinase activation *in vitro* with an IC₅₀ of 0.0013 μM. It also prevented the proliferation of human colon adenocarcinoma HT-29 cells with an IC₅₀ of 1.3 μM.

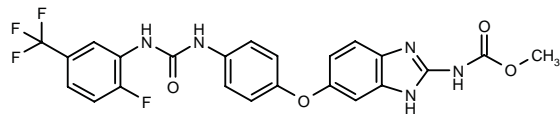
SOURCE – AstraZeneca.

REFERENCES

1. Boyle, F.T. et al. (AstraZeneca AB;AstraZeneca plc) *Substd. quinolines as antitumor agents*. WO 0244166.

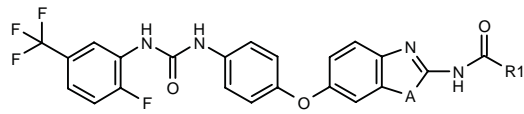
322465

N-[6-[4-[3-[2-Fluoro-5-(trifluoromethyl)phenyl]ureido]-phenoxy]-1*H*-benzimidazol-2-yl]carbamic acid methyl ester

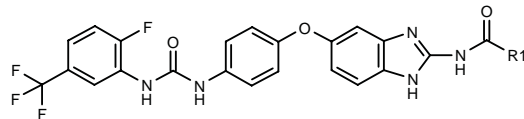


C23 H17 F4 N5 O4; Mol wt: 503.4103

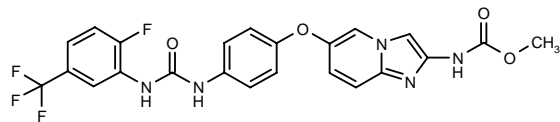
ACTION – Agent with the ability to inhibit Tie-2 and VEGFR-2 kinase activity with pIC₅₀ values > 7.0. Potentially useful for the treatment of cancer. Other exemplified compounds are:



Compound	R1	A	Formula
322466	OEt	NH	C24H19F4N5O4
322467	t-BuO	NH	C26H23F4N5O4
322468	Me	NH	C23H17F4N5O3
322469	CH2OMe	NH	C24H19F4N5O4
322470	CH2OCH2CH2OCH2CH2OMe	NH	C28H27F4N5O6
322478	OMe	O	C23H16F4N4O5



Compound	R1	Formula
322472	OCH2CH2N(Me)2	C26H24F4N6O4
322473	3-Pyr-CH2CH2	C28H22F4N6O3
322474	(CH2)3N(Me)2	C27H26F4N6O3
322475	1-Me-4-imidazolyl-CH2	C27H21F4N7O3
322476	4-Me-1-Piz-CH2	C28H27F4N7O3
322477	CH2N(Me)2	C25H22F4N6O3



322471: C23 H17 F4 N5 O4

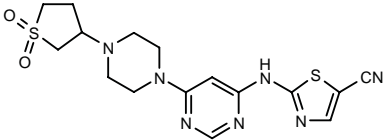
SOURCE – GlaxoSmithKline.

REFERENCES

1. Cheung, M. et al. (GlaxoSmithKline plc;GlaxoSmithKline KK) *Chemical cpds.* WO 0244156.

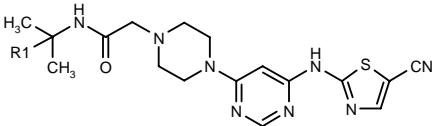
322775

2-[6-[4-(1,1-Dioxotetrahydrothien-3-yl)piperazin-1-yl]-pyrimidin-4-ylamino]thiazole-5-carbonitrile



C16 H19 N7 O2 S2; Mol wt: 405.5051

ACTION – Inhibitor of receptor and nonreceptor tyrosine kinases, potentially useful for the treatment of cancer, angiogenesis, ocular diseases such as retinal vascularization, diabetic retinopathy and age-related macular degeneration, inflammatory disorders including rheumatoid arthritis, psoriasis, contact dermatitis and delayed hypersensitivity reactions, and also osteosarcoma, osteoarthritis and rickets. Other specifically claimed compounds are:



Compound	R1	Formula
322776	Me	C ₁₈ H ₂₄ N ₈ OS
322777	H	C ₁₇ H ₂₂ N ₈ OS

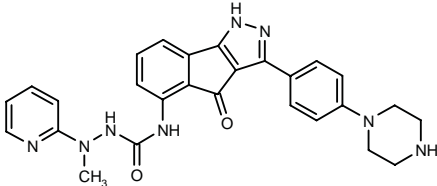
SOURCE – Merck & Co.

REFERENCES

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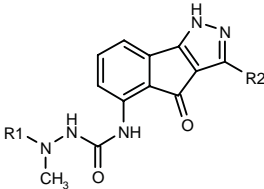
322928

1-Methyl-4-[4-oxo-3-[4-(1-piperazinyl)phenyl]-1,4-dihydro-indeno[1,2-c]pyrazol-5-yl]-1-(2-pyridyl)semicarbazide



C27 H26 N8 O2; Mol wt: 494.5564

ACTION – Cyclin-dependent kinase (CDK) inhibitor, potentially useful for the treatment of cancer, viral infections and other proliferative disorders including Alzheimer's disease, autoimmune diseases, fungal infections, psoriasis, vascular smooth cell proliferation associated with atherosclerosis, pulmonary fibrosis, arthritis, glomerulonephritis, neurodegenerative disorders and restenosis. Other specifically claimed semicarbazides include the following:



Compound	R1	R2	Formula
322929	4-Pyr	4-(1-Piz)-Ph	C ₂₇ H ₂₆ N ₈ O ₂
322930	2-pyrazinyl	4-(1-Piz)-Ph	C ₂₆ H ₂₅ N ₈ O ₂
322932	3-Pyr	4-(1-Piz)-Ph	C ₂₇ H ₂₆ N ₈ O ₂
322933	4-THP	4-(1-Piz)-Ph	C ₂₇ H ₃₁ N ₇ O ₃
322935	4-THP	4-(4-Me-1-Piz)-Ph	C ₂₈ H ₃₃ N ₇ O ₃
322937	cyclohexyl	4-(4-Me-1-Piz)-Ph	C ₂₉ H ₃₆ N ₇ O ₂
322938	4-THP	4-(perhydro-1,4-diazepin-1-yl)-Ph	C ₂₈ H ₃₃ N ₇ O ₃
322940	4-THP	2,4-(Me)2-5-thiazolyl	C ₂₂ H ₂₄ N ₆ O ₃ S

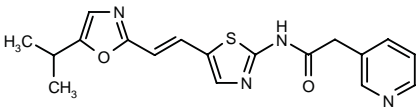
SOURCE – Bristol-Myers Squibb.

REFERENCES

1. Carini, D.J. (Bristol-Myers Squibb Co.) *Semicarbazides and their use as cyclin dependent kinase inhibitors.* WO 0246182.

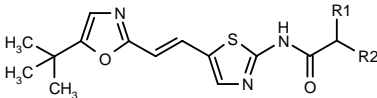
323002

N-[5-[(E)-2-(5-Isopropylloxazol-2-yl)vinyl]thiazol-2-yl]-2-(3-pyridyl)acetamide



C18 H18 N4 O2 S; Mol wt: 354.4322

ACTION – Inhibitor of cyclin-dependent kinases (CDKs), potentially useful for the treatment of proliferative disorders such as cancer and arthritis, as well as Alzheimer's disease and cardiovascular disorders. Other specifically claimed 2-aminothiazole derivatives include the following:



Compound	R1	R2	Isomer	Formula
323003	5-imidazolyl	H		C ₁₇ H ₁₉ N ₅ O ₂ S
323004	4-imidazolyl-CH2	NHAc		C ₂₀ H ₂₄ N ₆ O ₃ S
323005	4-imidazolyl-CH2	NH2	S	C ₁₈ H ₂₂ N ₆ O ₂ S
323006	2-Me-3-Pyr	H		C ₂₀ H ₂₂ N ₄ O ₂ S
323007	3-Pyr	Me		C ₂₀ H ₂₂ N ₄ O ₂ S
323008	1-pyrazolyl	H		C ₁₇ H ₁₉ N ₅ O ₂ S
323009	4,5-(CN)2-1-imidazolyl	H		C ₁₉ H ₁₇ N ₇ O ₂ S
323010	2-Me-1-imidazolyl	H		C ₁₈ H ₂₁ N ₅ O ₂ S

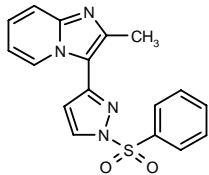
SOURCE – Bristol-Myers Squibb.

REFERENCES

1. Rawlins, D.B. et al. (Bristol-Myers Squibb Co.) *Carbon substd. aminothiazole inhibitors of cyclin dependent kinases.* US 6407124.

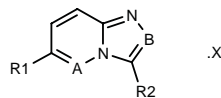
323064

2-Methyl-3-[1-(phenylsulfonyl)-1*H*-pyrazol-3-yl]imidazo-[1,2-*a*]pyridine



C17 H14 N4 O2 S; Mol wt: 338.3896

ACTION – Phosphatidylinositol 3-kinase (PI3K) inhibitor with potential as an antitumor agent. Other exemplified imidazopyridine derivatives are:



Compound	R1	R2	A	B	X	Formula
323065	Cl	1-[5-Cl-1,3-(Me)2-4-pyrazolyl-SO2]-3-pyrazolyl	CH	C(Me)		C ₁₈ H ₁₄ Cl ₂ N ₆ O ₂ S
323066	Br	2-Me-5-(CO2Na)-PhSO2N(Me)N=CH	CH	CH		C ₁₇ H ₁₄ BrN ₄ NaO ₄ S
323067	Br	4-Me-5-(2-Me-4-NO2-PhS)-4H-1,2,4-triazol-3-yl	CH	C(Me)	HCl	C ₁₈ H ₁₅ BrN ₆ O ₂ S.HCl
323068	Cl	2-(2-MeO-5-NO2-PhCH2S)-4-thiazolyl	CH	CH		C ₁₈ H ₁₃ ClN ₄ O ₃ S ₂
323069	Br	4-Me-3-Pyr-SO2N(Me)N=CH	CH	CH	2HCl	C ₁₅ H ₁₄ BrN ₅ O ₂ S.2HCl
323070	Br	2-(2-Me-4-NO2-PhSO)-4-thiazolyl	CH	CH	HCl	C ₁₇ H ₁₁ BrN ₄ O ₃ S ₂ .HCl
323071	Cl	3-(4-MeO-PhCH2S)-Ph	N	N		C ₁₉ H ₁₅ ClN ₄ OS
323072	Cl	2-(2-Me-5-NO2-PhSO2)-4-imidazolyl	CH	CH		C ₁₇ H ₁₂ ClN ₅ O ₄ S

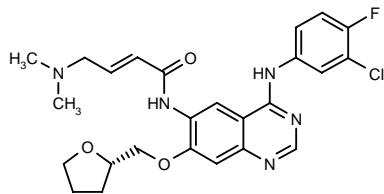
SOURCES – Imperial Cancer Research Technology; Ludwig Institute for Cancer Research, New York, NY (US); Yamanouchi.

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1. Hayakawa, M. et al. (Yamanouchi Pharmaceutical Co., Ltd.;Ludwig Institute for Cancer Research; Imperial Cancer Research Technology, Ltd.) *Imidazopyridine derivs.* US 6403588.

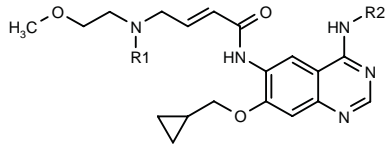
323390

N-[4-(3-Chloro-4-fluorophenylamino)-7-[tetrahydrofuran-2(*S*)-ylmethoxy]quinazolin-6-yl]-4-(dimethylamino)-2-butenamide

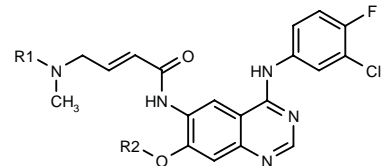


C25 H27 Cl F N5 O3; Mol wt: 499.9713

ACTION – Inhibitor of epidermal growth factor receptor (EGFR) tyrosine kinase (IC₅₀ = 0.3 nM against human enzyme), potentially useful for the treatment of cancer, as well as respiratory, gastrointestinal and gallbladder disorders. Other exemplified quinazoline derivatives are:



Compound	R1	R2	Formula
323391	Me	3-Cl-4-F-Ph	C ₂₆ H ₂₉ ClFN ₅ O ₃
323394	CH2CH2OMe	(R)-CH(Me)Ph	C ₃₀ H ₃₉ N ₅ O ₄
323396	Me	(R)-CH(Me)Ph	C ₂₈ H ₃₈ N ₅ O ₃



Compound	R1	R2	Formula
323392	Me	cyclopentyl	C ₂₅ H ₂₇ ClFN ₅ O ₂
323397	Me	3(S)-THF	C ₂₄ H ₂₆ ClFN ₅ O ₃
323398	cyclopropyl	cyclopentyl	C ₂₇ H ₂₉ ClFN ₅ O ₂
323399	Et	3(S)-THF	C ₂₅ H ₂₇ ClFN ₅ O ₃
323400	i-Pr	3(S)-THF	C ₂₆ H ₂₉ ClFN ₅ O ₃

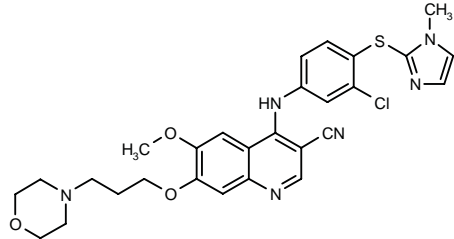
SOURCE – Boehringer Ingelheim.

REFERENCES

1. Himmelsbach, F. et al. (Boehringer Ingelheim Pharma KG) *Quinazoline derivs., medicaments containing said cpds., their utilization and method for the production thereof.* DE 10063435, WO 0250043.

323664

4-[3-Chloro-4-(1-methyl-1*H*-imidazol-2-ylsulfanyl)phenyl-amino]-6-methoxy-7-[3-(4-morpholinyl)propoxy]quinoline-3-carbonitrile



C28 H29 Cl N6 O3 S; Mol wt: 565.0951

ACTION – Potent MEK1 kinase inhibitor (IC₅₀ = 2 nM in the Raf/MEK1 assay) able to inhibit MEK1 and mitogen-activated protein kinase (MAPK) phosphorylation with respective IC₅₀ values of 8 and 0.01 nM. In addition, it inhibited the proliferation of human colon carcinoma LoVo cells (IC₅₀ = 5 nM).

SOURCE – Wyeth.

REFERENCES

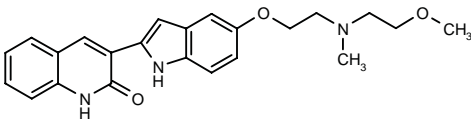
1. Wissner, A. et al. (American Cyanamid Co.) *Substd. 3-cyanoquinolines as protein tyrosine kinase inhibitors*. EP 1117659, WO 0018761.

2. Wissner, A. et al. (American Cyanamid Co.) *Substd. 3-cyanoquinolines*. US 6288082.

3. Berger, D.M. et al. *Synthesis and evaluation of 4-anilino substituted 3-quinoline-carbonitriles as inhibitors of kinases of the Ras-MAPK signaling cascade*. 224th ACS Natl Meet (Aug 18-22, Boston) 2002, Abst MEDI 105.

323756

3-[5-[2-[N-(2-Methoxyethyl)-N-methylamino]ethoxy]-1H-indol-2-yl]quinolin-2(1H)-one



C23 H25 N3 O3; Mol wt: 391.4685

ACTION – Potent vascular endothelial growth factor receptor-2 (VEGFR-2, KDR) tyrosine kinase inhibitor with strong activity against KDR kinase (IC₅₀ = 7 nM), as well as Flt-1, Flt-3 and Flt-4 kinases (IC₅₀ = 14, 0.5 and 1.6 nM, respectively). It was also active in a cell-based KDR autophosphorylation assay (IC₅₀ = 9 nM), as well as in preventing KDR autophosphorylation in mouse lung. In addition, compound dose-dependently inhibited the growth of fibrosarcoma HT-1080 fibrosarcoma in a mouse xenograft model.

SOURCE – Merck & Co.

REFERENCES

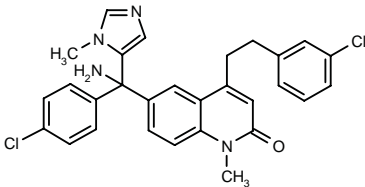
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2. Fraley, M.E. et al. (Merck & Co., Inc.) *Orally active salts with tyrosine kinase activity*. WO 0232861.

3. Fraley, M.E. et al. *Discovery, synthesis, SAR, and in vitro/in vivo characterization of a novel quinolinone class of VEGFR-2 kinase inhibitors*. 224th ACS Natl Meet (Aug 18-22, Boston) 2002, Abst MEDI 221.

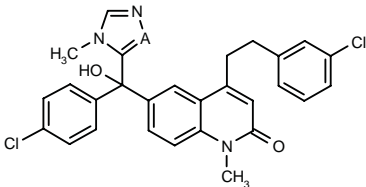
323832

6-[1-Amino-1-(4-chlorophenyl)-1-(1-methyl-1H-imidazol-5-yl)methyl]-4-[2-(3-chlorophenyl)ethyl]-1-methylquinolin-2(1H)-one

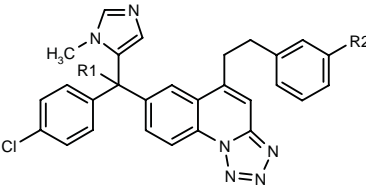


C29 H26 Cl2 N4 O; Mol wt: 517.4574

ACTION – Antitumor agent reported to possess protein farnesyltransferase-inhibitory properties. Other specifically claimed compounds from this series of quinoline derivatives include the following:



Compound	A	Formula
323833	CH	C ₂₈ H ₂₅ Cl ₂ N ₃ O ₂
323837	N	C ₂₈ H ₂₄ Cl ₂ N ₄ O ₂



Compound	R1	R2	Formula
323834	NH2	Cl	C ₂₈ H ₂₂ Cl ₂ N ₇
323835	NHAc	Cl	C ₃₀ H ₂₅ Cl ₂ N ₇ O
323836	NHAc	H	C ₃₀ H ₂₆ ClN ₇ O

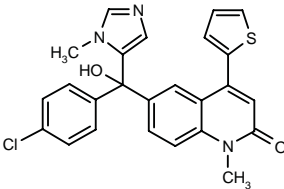
SOURCE – Janssen.

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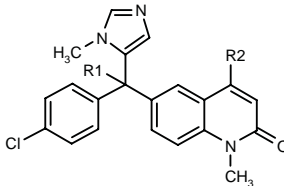
323838

6-[1-(4-Chlorophenyl)-1-hydroxy-1-(1-methyl-1H-imidazol-5-yl)methyl]-1-methyl-4-(2-thienyl)quinolin-2(1H)-one



C25 H20 Cl N3 O2 S; Mol wt: 461.9710

ACTION – Antitumor agent reported to possess protein farnesyltransferase-inhibitory properties. Other specifically claimed compounds from this series of quinoline derivatives include the following:



Compound	R1	R2	Formula
323839	OH	3-Pyr	C ₂₆ H ₂₁ ClN ₄ O ₂
323840	OH	4-Me-2-thiazolyl	C ₂₆ H ₂₁ ClN ₄ O ₂ S
323841	NHAc	4-Ph-2-thiazolyl	C ₃₂ H ₂₆ ClN ₅ O ₂ S
323842	NH2	5-Cl-2-thienyl-CH2CH2	C ₂₇ H ₂₄ Cl ₂ N ₄ OS

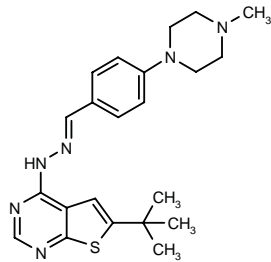
SOURCE – Janssen.

REFERENCES

1. Angibaud, P.R. et al. (Janssen Pharmaceutica NV) *Farnesyl transferase inhibiting 4-heterocyclyl-quinoline and quinazoline derivs.* WO 0251834.

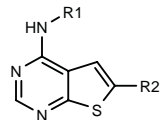
323996

4-(4-Methylpiperazin-1-yl)benzaldehyde (6-*tert*-butyl-thieno[2,3-*d*]pyrimidin-4-yl)hydrazone

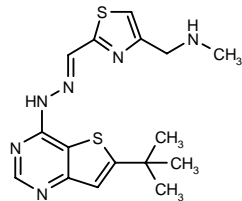


C22 H28 N6 S; Mol wt: 408.5712

ACTION – Cyclin-dependent kinase 4 (CDK4) inhibitor that gave IC₅₀ values of 0.096 and 1.0 µg/ml when tested for inhibition of CDK4 and CDK2, respectively. This compound demonstrated antitumor activity against human colon cancer HCT 116 cells. Other exemplified compounds include the following:



Compound	R1	R2	Formula
323997	2-oxo-2,3-dihydro-3-indolylidene=N	t-Bu	C ₁₈ H ₁₇ N ₅ OS
323998	6-(cyclopropyl-NHCH2)-2-Pyr-CH=N	t-Bu	C ₂₀ H ₂₄ N ₆ S
323999	5-(MeNHCH2)-2-thiazolyl-CH=N	t-Bu	C ₁₆ H ₂₀ N ₆ S ₂
324000	4-[NH2CH(Me)]-2-thiazolyl-CH=N	t-Bu	C ₁₆ H ₂₀ N ₆ S ₂
324001	5-(MeNHCH2)-2-thiazolyl-CH=N	CH(Me)Et	C ₁₆ H ₂₀ N ₆ S ₂
324008	2-Pyr-CH=N	t-BuSi(Ph)2-OCH2	C ₂₉ H ₂₉ N ₅ OSSi



324002: C16 H20 N6 S2

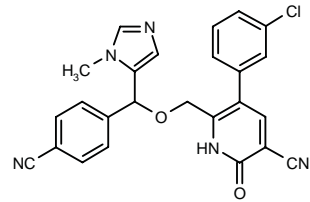
SOURCE – Daiichi Pharmaceutical.

REFERENCES

1. Uoto, K. et al. (Daiichi Pharmaceutical Co., Ltd.) *CDK4 inhibitors.* WO 0251849.

324092

5-(3-Chlorophenyl)-6-[1-(4-cyanophenyl)-1-(1-methyl-1*H*-imidazol-5-yl)methoxymethyl]-2-oxo-1,2-dihydropyridine-3-carbonitrile



C25 H18 Cl N5 O2; Mol wt: 455.9032

ACTION – Protein farnesyltransferase inhibitor (IC₅₀ = 0.82 nM) with high selectivity over protein geranylgeranyltransferase (IC₅₀ = 820 nM) and acceptable Q-T prolongation in the Purkinje fiber assay. Potentially useful as an antineoplastic agent.

SOURCE – Abbott.

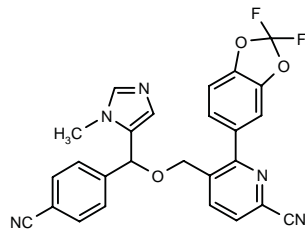
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A-373857

323665

5-[1-(4-Cyanophenyl)-1-(1-methyl-1*H*-imidazol-5-yl)-methoxymethyl]-6-(2,2-difluoro-1,3-benzodioxol-5-yl)-pyridine-2-carbonitrile



C26 H17 F2 N5 O3; Mol wt: 485.4483

ACTION – Potent inhibitor of protein farnesyltransferase (IC₅₀ = 0.18 nM) with high selectivity versus protein geranylgeranyltransferase (IC₅₀ = 1100 nM) and able to block Ras cellular processing with an EC₅₀ value of 1.2 nM. Compound exhibited good oral bioavailability in dogs and monkeys (F = 90 and 56%, respectively). Potentially useful as an antineoplastic agent.

SOURCE – Abbott.

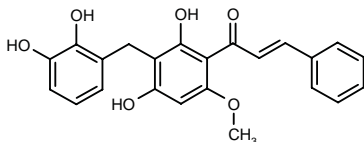
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2. Tong, Y. et al. *Discovery of potent and orally active farnesyltransferase inhibitors.* 224th ACS Natl Meet (Aug 18-22, Boston) 2002, Abst MEDI 129.

KLAINETIN B

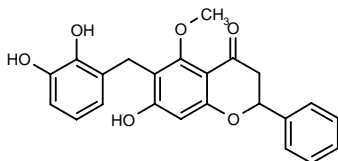
322762

1-[3-(2,3-Dihydroxybenzyl)-2,4-dihydroxy-6-methoxy-phenyl]-3-phenyl-2-propen-1-one



C23 H20 O6; Mol wt: 392.4050

ACTION – Cytostatic compound isolated from extracts of the plant *Uvaria klaineri*, reported to display inhibitory activity against cyclin-dependent kinases (CDKs) and other protein kinases such as KDR; it demonstrated inhibitory activity against CDK4 ($IC_{50} = 1.14 \mu M$), CDK2 ($IC_{50} = 6.04 \mu M$) and KDR ($IC_{50} = 6.48 \mu M$). Potentially useful for the treatment of cancer. Another compound from the same source is:



Klainetin A [322763]: C23 H20 O6

SOURCE – Aventis Pharma.

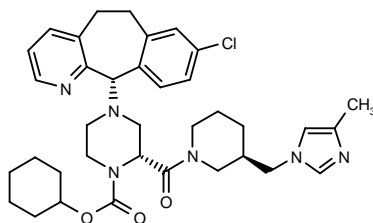
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SCH-400

323754

4-[8-Chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11(S)-yl]-2(R)-[3(S)-(4-methyl-1H-imidazol-1-ylmethyl)piperidin-1-ylcarbonyl]piperazine-1-carboxylic acid cyclohexyl ester



C36 H45 Cl N6 O3; Mol wt: 645.2435

ACTION – Antineoplastic agent, a potent protein farnesyl-transferase inhibitor ($IC_{50} = 0.08 \text{ nM}$) with > 46,000-fold selectivity over protein geranygeranyltransferase. It inhibited *in vitro* tumor cell growth in the picomolar range and was orally bioavailable in rats, mice and monkeys; in mouse xenograft models, it inhibited tumor growth up to 99%.

SOURCE – Schering-Plough.

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ANGIOGENESIS INHIBITORS

E4G10

321959

Monoclonal antibody against the N-terminal region (amino acid residues 46-60) of vascular endothelial cadherin (VE cadherin)

ACTION – Antiangiogenic agent, a monoclonal antibody (MAb) that selectively targets vascular endothelial cadherin (VE cadherin), resulting in selective inhibition of VE cadherin function during angiogenesis, but does not disrupt normal vasculature. The antibody inhibited vascular tube formation in Matrigel plug and corneal micropocket assays in mice and tumor growth in murine tumor and human tumor xenograft models in mice via an antiangiogenic mechanism by decreasing microvessel density and tumor cell proliferation, increasing tumor and endothelial cell apoptosis. Moreover, the MAb specifically targets a subset of tumor endothelium undergoing active proliferation.

SOURCE – ImClone Systems.

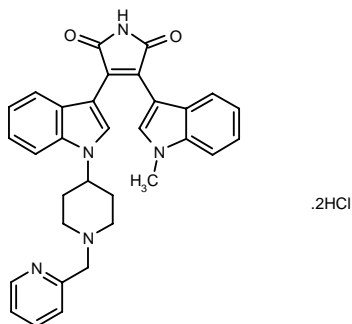
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LY-317615.2HCl

306147

3-(1-Methyl-1*H*-indol-3-yl)-4-[1-[1-(pyridin-2-ylmethyl)-piperidin-4-yl]-1*H*-indol-3-yl]-1*H*-pyrrole-2,5-dione dihydrochloride



C32 H29 N5 O2 . 2HCl; Mol wt: 588.5359

ACTION – Selective, small-molecule inhibitor of protein kinase C β (PKC β ; IC₅₀ = 0.03 μ M) with selective growth-inhibitory activity against vascular endothelial growth factor (VEGF)-induced human umbilical vein endothelial cell (HUVEC) proliferation (IC₅₀ = 150 nM) relative to human tumor cells. It inhibited growth factor-stimulated neovascularization in the rat cornea micropocket assay when given at a dose of 10 mg/kg p.o. b.i.d. for 10 days. Moreover, compound produced marked inhibition of tumor vascularization in a range of human solid tumor xenografts and it was effective both as a single agent and in combination with cytotoxic therapies in brain, breast, ovarian, non-small cell lung, small cell lung, gastric, hepatocellular, colon and renal cell cancer xenografts. Additive activity was generally seen in combination with cytotoxic agents. Results of an ongoing phase I trial in patients with solid tumors receiving escalating single oral doses of compound (20-350 mg) showed no dose-limiting toxicity at up to 160 mg; the most frequent adverse event has been grade 1 fatigue. At these doses, the half-life of compound was 9-25 h, with no significant accumulation. Disease stabilization was achieved in 4 of 27 patients treated with over 4 cycles, and 3 of these have received over 6 cycles.

SOURCE – Lilly.

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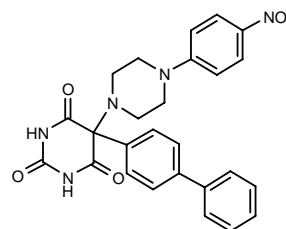
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RO-28-2653*

254074

5-(4-Biphenyl)-5-[4-(4-nitrophenyl)piperazin-1-yl]-barbituric acid

5-(4-Biphenyl)-5-[4-(4-nitrophenyl)piperazin-1-yl]-pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione



C26 H23 N5 O5; Mol wt: 485.4977

ACTION – Potent and selective matrix metalloproteinase (MMP) inhibitor with high selectivity for MMP-2 (gelatinase A; IC₅₀ = 10 nM), MMP-9 (gelatinase B; IC₅₀ = 12 nM), MMP-14 (membrane type 1 MMP; IC₅₀ = 10 nM) and MMP-8 (neutrophil collagenase; IC₅₀ = 12 nM) over MMP-3 (stromelysin 1; IC₅₀ = 1200 nM) and MMP-1 (interstitial collagenase; IC₅₀ = 1200 nM). Compound demonstrated antiangiogenic activity and was also able to induce apoptosis in R3327 Dunning prostate tumor cells, and to impair mitochondrial function at high concentrations. In rats bearing Dunning prostate tumors, it dose-dependently (10-300 mg/kg/day p.o.) reduced tumor weight by up to 90%, even in the case of established tumors, and it also significantly prolonged survival. Inhibition of tumor growth was also been obtained in other models, i.e., human fibrosarcoma HT-1080, breast carcinoma MDA-MB-231, melanoma A2058 and lung H460 xenografts.

SOURCE – Roche.

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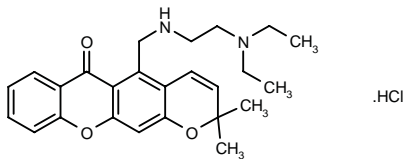
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*Identified compound **254074** Drug Data Rep 1997, 019(10): 0931.

OTHER ONCOLYTIC DRUGS

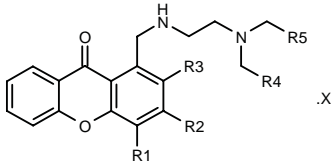
321866

5-[2-(Diethylamino)ethylaminomethyl]-2,2-dimethyl-2H,6H-pyrano[3,2-b]xanthen-6-one hydrochloride



C25 H30 N2 O3 . HCl; Mol wt: 442.9839

ACTION – Cytotoxic agent shown to inhibit the proliferation of human lung adenocarcinoma A549 cells (IC₅₀ = 8 µM), human colon adenocarcinoma HT-29 cells (IC₅₀ = 2 µM) and mouse leukemia L1210 cells (IC₅₀ = 2 µM). Compound blocked cell cycle in the S phase, in accordance with its DNA-binding potency (EC₅₀ = 30 µM). Other related compounds are:



Compound	R1	R2	R3	R4	R5	X	Formula
321863	-CH=CHC(Me)2O-	H	H	H	H	HCl	C ₂₃ H ₂₆ N ₂ O ₃ ·HCl
321864	-CH=CHC(Me)2O-	H	Me	Me	Me	fumarate	C ₂₅ H ₃₀ N ₂ O ₃ ·C ₄ H ₄ O ₄
321865	H	-OC(Me)2CH=CH-	H	H	H	HCl	C ₂₃ H ₂₆ N ₂ O ₃ ·HCl

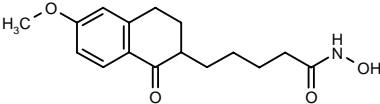
SOURCES – University of Athens, Athens (GR); NCSR Demokritos, Greece (GR).

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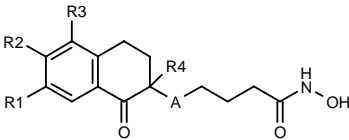
322745

5-(6-Methoxy-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)-pentanohydroxamic acid



C16 H21 N O4; Mol wt: 291.3449

ACTION – Histone deacetylase (HDAC) inhibitor considered to have potential as an antitumor agent. Other specifically claimed tetralone derivatives are:



Compound	R1	R2	R3	R4	A	Formula
322746	H	H	H	H	-CH2-	C ₁₅ H ₁₉ NO ₃
322747	H	Cl	H	H	-(CH2)2-	C ₁₆ H ₂₀ ClNO ₃
322748	H	H	H	Me	-(CH2)2-	C ₁₇ H ₂₃ NO ₃
322749	H	H	H	H	-(CH2)2-	C ₁₆ H ₂₁ NO ₃
322750	H	H	H	Me	-CH2-	C ₁₆ H ₂₁ NO ₃
322752	H	H	H	Me	-CH=CH-	C ₁₇ H ₂₁ NO ₃
322753	H	H	OMe	H	-(CH2)2-	C ₁₇ H ₂₃ NO ₄
322755	H	H	OMe	CO2Et	-(CH2)2-	C ₂₀ H ₂₇ NO ₆
322759	Me	H	Me	CO2Et	-(CH2)4-	C ₂₃ H ₃₃ NO ₅
322761	Cl	H	H	Me	-(CH2)2-	C ₁₇ H ₂₂ ClNO ₃

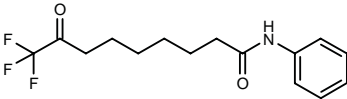
SOURCE – Roche.

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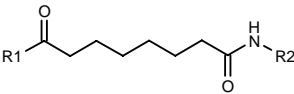
322816

9,9,9-Trifluoro-8-oxo-N-phenylnonanamide

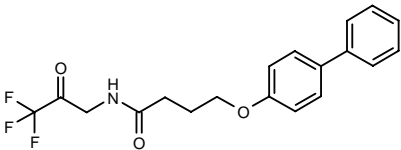


C15 H18 F3 N O2; Mol wt: 301.3062

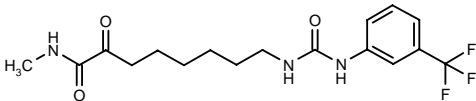
ACTION – Inhibitor of histone deacetylase expected to be useful for the treatment of cancer. Other exemplified compounds are:



Compound	R1	R2	Formula
322817	CF3	4-Cl-Ph	C ₁₅ H ₁₇ ClF ₃ NO ₂
322818	CF3	4-NH2-PhCH2	C ₁₆ H ₂₁ F ₃ N ₂ O ₂
322820	CONHMe	3-Ph-Ph	C ₂₂ H ₂₆ N ₂ O ₃
322821	CONHMe	2-Naph	C ₂₀ H ₂₄ N ₂ O ₃
322822	CONHMe	4-(4-EtO-Ph)-2-thiazolyl	C ₂₁ H ₂₇ N ₃ O ₄ S
322824	CONHMe	NHCOPh	C ₁₇ H ₂₃ N ₃ O ₄



322819: C₁₉ H₁₈ F₃ N O₃



322823: C₁₇ H₂₂ F₃ N₃ O₃

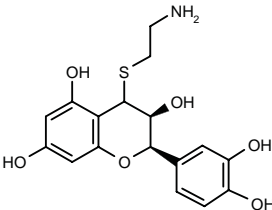
SOURCE – Abbott.

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323623

4-(2-Aminoethylsulfanyl)-2(R)-(3,4-dihydroxyphenyl)-3,4-dihydro-2H-1-benzopyran-3(S),5,7-triol



C₁₇ H₁₉ N O₆ S; Mol wt: 365.4041

ACTION – Synthetic epicatechin derivative with anti-oxidant and free radical-scavenging activity. Potentially useful for the treatment of cancer, cardiovascular diseases and age-related disorders.

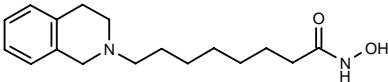
SOURCE – CSIC, Madrid (ES).

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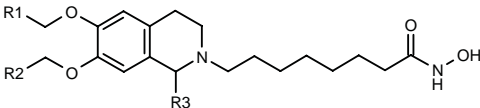
323638

8-(1,2,3,4-Tetrahydroisoquinolin-2-yl)octanohydroxamic acid

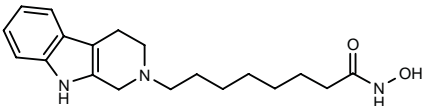


C₁₇ H₂₆ N₂ O₂; Mol wt: 290.4044

ACTION – Histone deacetylase (HDAC) inhibitor (54% inhibition at 10 nM) expected to be useful for the treatment of proliferative disorders such as cancer. Other exemplified tetrahydropyridine derivatives are:



Compound	R1=R2	R3	Formula
323639	Me	H	C ₂₁ H ₃₄ N ₂ O ₄
323640	H	Ph	C ₂₈ H ₃₄ N ₂ O ₄



323641: C₁₉ H₂₇ N₃ O₂

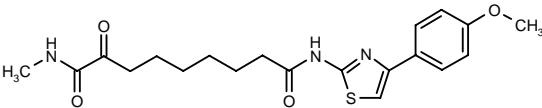
SOURCE – Roche.

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1. Georges, G. et al. (F. Hoffmann-La Roche AG) *Tetrahydropyridine derivs., their preparation and their use as cell proliferation inhibitors*. WO 0251842.

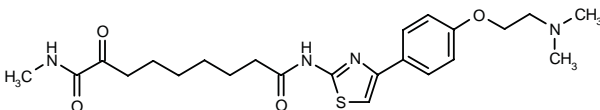
323666

N⁹-[4-(4-Methoxyphenyl)thiazol-2-yl]-N¹-methyl-2-oxo-nonanediamide



C₂₀ H₂₅ N₃ O₄ S; Mol wt: 403.5005

ACTION – Antineoplastic agent, a histone deacetylase inhibitor (IC₅₀ = 9 nM) with cytotoxic activity against human breast cancer MDA-435 cells and human fibro-sarcoma HT-1080 cells (IC₅₀ = 4.1 and 1.2 μM, respectively). In mice bearing HT-1080 sarcomas, significant, dose-related antitumor activity was seen at 30 and 100 mg/kg i.p. Another related compound is:



323667: C₂₃ H₃₂ N₄ O₄ S

SOURCE – Abbott.

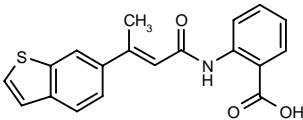
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2. Frey, R.R. et al. *Electrophilic ketone-based histone deacetylase inhibitors as cancer chemotherapeutic agents*. 224th ACS Natl Meet (Aug 18-22, Boston) 2002, Abst MEDI 121.

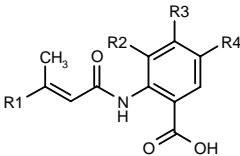
323733

2-[3-(1-Benzothien-6-yl)-2(E)-butenamido]benzoic acid



C19 H15 N O3 S; Mol wt: 337.3975

ACTION – Antitumor agent with telomerase-inhibitory properties (> 50% at 5 µM). Other exemplified carbox-amides are:



Compound	R1	R2	R3	R4	Formula
323734	5-benzothienyl	H	H	H	C ₁₉ H ₁₅ NO ₃ S
323735	6-benzothienyl	H	OMe	OMe	C ₂₁ H ₁₉ NO ₅ S
323736	6-benzothienyl	Me	H	H	C ₂₀ H ₁₇ NO ₃ S
323737	6-benzothienyl	H	H	F	C ₁₉ H ₁₄ FNO ₃ S
323738	6-quinolyl	H	H	H	C ₂₀ H ₁₆ N ₂ O ₃

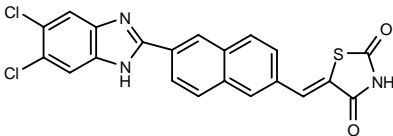
SOURCE – Boehringer Ingelheim.

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1. Huel, N. et al. (Boehringer Ingelheim Pharma KG) *Carboxamides for use as telomerase inhibitors*. DE 10065043, WO 0251830.

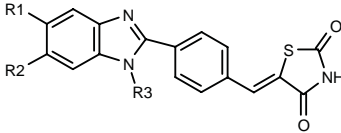
323785

5-[6-(5,6-Dichloro-1 H-benzimidazol-2-yl)naphthalen-2-ylmethylene]thiazolidine-2,4-dione

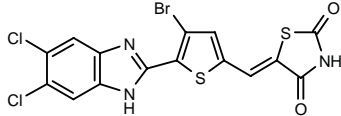


C21 H11 Cl2 N3 O2 S; Mol wt: 440.3089

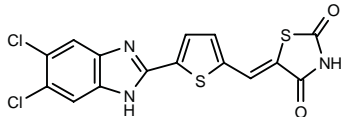
ACTION – Telomerase inhibitor (IC₅₀ = 0.29-0.55 µM), potentially useful for the treatment of cancer. Other exemplified thiazolidinedione compounds are:



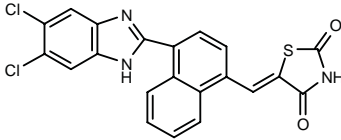
Compound	R1=R2	R3	Formula
323786	Cl	H	C ₁₇ H ₉ Cl ₂ N ₃ O ₂ S
323787	H	H	C ₁₇ H ₁₁ N ₃ O ₂ S
323788	H	3,4-(Cl)2PhCH2	C ₂₄ H ₁₆ Cl ₂ N ₃ O ₂ S



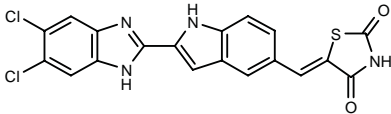
323789: C15 H6 Br Cl2 N3 O2 S2



323790: C15 H7 Cl2 N3 O2 S2



323791: C21 H11 Cl2 N3 O2 S



323792: C19 H10 Cl2 N4 O2 S

SOURCES – Geron; Kyowa Hakko.

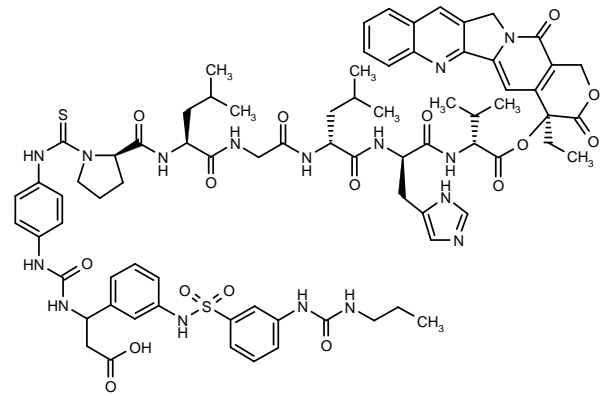
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323849

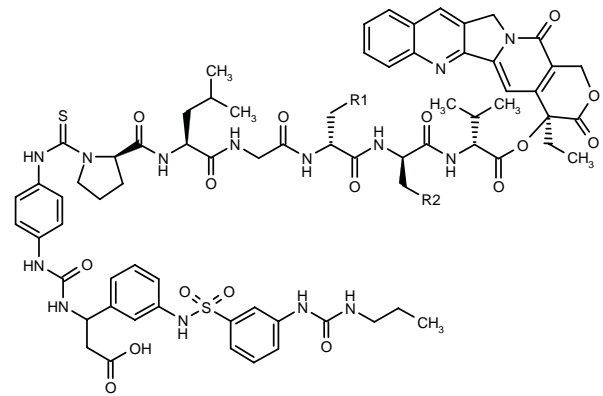
1-[4-[3-[2-Carboxy-1-[3-[3-(3-propylureido)phenyl-sulfonamido]phenyl]ethyl]ureido]phenylaminocarbonothio-yl]-D-prolyl-L-leucyl-glycyl-D-leucyl-D-histidyl-D-valine 4(S)-ethyl-3,14-dioxo-3,4,12,14-tetrahydro-1*H*-pyrano-[3',4':6,7]indolizino[1,2-*b*]quinolin-4-yl ester

20-(*S*)-*O*-[1-[4-[3-[2-Carboxy-1-[3-[3-(3-propylureido)-phenylsulfonamido]phenyl]ethyl]ureido]phenylamino]car-bonothioyl]-D-prolyl-L-leucyl-glycyl-D-leucyl-D-histidyl-D-valyl]camptothecin



C77 H92 N16 O16 S2; Mol wt: 1561.8020

ACTION – A conjugate of an integrin receptor antagonist and a cytostatic agent that is selectively cleaved by enzymes found in tumor tissues such as matrix metallo-proteases, resulting in a tumor-specific activity. The compound gave an IC₅₀ value of 25 nM in an integrin α_vβ₃ binding test and exhibited cytotoxic activity against human colon cancer SW480 and HT-29 cells (IC₅₀ = 100 and 180 nM, respectively) and murine melanoma B16F10 cells (IC₅₀ = 500 nM). Compound also demonstrated antitumor activity in mice bearing human melanoma xenografts. Other exemplified compounds are:



Compound	R1	R2	Formula
323850	i-Pr	CONH2	C ₇₅ H ₉₁ N ₁₅ O ₁₇ S ₂
323851	SMe	5-imidazolyl	C ₇₅ H ₈₈ N ₁₆ O ₁₆ S ₃

SOURCE – Bayer.

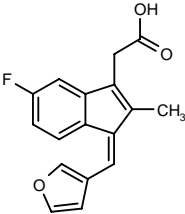
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IND-12

320500

2-[(*Z*)-5-Fluoro-1-(furan-3-ylmethylidene)-2-methyl-1*H*-inden-3-yl]acetic acid



C17 H13 F O3; Mol wt: 284.2847

ACTION – Sulindac derivative able to reverse the pheno-type of *ras*-transformed MDCK-f3 cells and to restore an untransformed epitheloid morphology in these cells. It inhibited the proliferation of H-*ras*-transformed epithelial MDCK cells significantly more potently (IC₅₀ = 50 μM) than nontransformed cells (IC₅₀ = 300 μM) and was more potent than sulindac (IC₅₀ = 320 and 300 μM, respectively). It was also more active than the parent compound in inhibiting cyclooxygenase activity (IC₅₀ = 0.24 μM) and the p21*ras*/Raf interaction (IC₅₀ = 30 μM). Its ability to inhibit the Ras pathway was confirmed by reductions in phosphorylated mitogen-activated protein kinases (MAPK) and in Ras-activated gene expression. Potentially useful as an antineoplastic agent.

SOURCES – Klinikum Kreis Herford, Herford (DE); Universität Konstanz, Konstanz (DE); Max-Planck-Institut für Molekulare Physiologie, Dortmund (DE); Squarix; Universitätsklinikum, Essen (DE).

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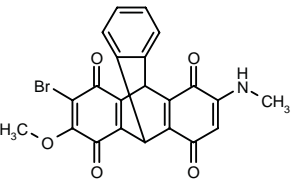
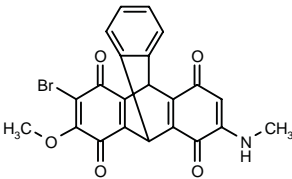
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TT-24

323608

Mixture of 2-bromo-3-methoxy-6-(methylamino)-1,4,5,8,9,10-hexahydro-9,10[1',2']-benzenoanthracene-1,4,5,8-tetraone and 2-bromo-3-methoxy-7-(methylamino)-1,4,5,8,9,10-hexahydro-9,10[1',2']-benzenoanthracene-1,4,5,8-tetraone



C22 H14 Br N O5; Mol wt: 452.2586

ACTION – Nucleoside transport inhibitor that induced apoptotic DNA fragmentation and decreased the viability of L1210 leukemia cells in the nanomolar range similar to daunorubicin ($IC_{50} = 48$ and 25 nM, respectively).

SOURCE – Kansas State University, Manhattan, KS (US).

REFERENCES

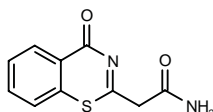
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MODULATORS OF THE THERAPEUTIC ACTIVITY OF ANTINEOPLASTIC AGENTS

ICX-56259537

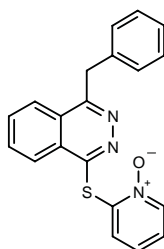
322463

2-(4-Oxo-4H-1,3-benzothiazin-2-yl)acetamide



C10 H8 N2 O2 S; Mol wt: 220.2512

ACTION – Poly(ADP-ribose)polymerase (PARP, NAD⁺ ADP-ribosyltransferase) inhibitor with an EC_{50} value of 40 μ M against PARP1 *in vitro* and displaying > 12-fold selectivity over PARP2. Potentially useful as a cytotoxin or a sensitizing agent in DNA-damaging therapies such as radiotherapy or chemotherapy. Another exemplified compound showed selective inhibition of PARP2 ($EC_{50} = 17$ μ M vs. 59.1 μ M for PARP1):



ICX-56258231 [322464]: C20 H15 N3 O S

SOURCE – Iconix.

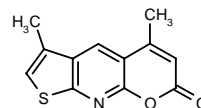
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RADIATION THERAPY

321779

4,6-Dimethyl-2H-pyrano[2,3-b]thieno[3,2-e]pyridin-2-one



C12 H9 N O2 S; Mol wt: 231.2741

ACTION – Photochemotherapeutic agent, a bioisostere of psoralen able to inhibit the growth of HeLa and HL-60 cells following exposure to UVA light with IC_{50} values of 8.9 and 2.2 μ M, respectively, without skin phototoxicity.

SOURCES – Consiglio Nazionale delle Ricerche, Roma (IT); Università degli Studi di Padova, Padova (IT).

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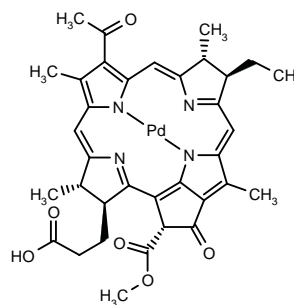
Pd-BACTERIOPHEOPHORBIDE*

291143

Hydrogen [(22*R*,7*R*,8*R*,17*S*,18*S*)-3-[12-acetyl-7-ethyl-22-(methoxycarbonyl)-3,8,13,17-tetramethyl-21-oxo-21,22,7,8,17,18-hexahydrocyclopenta[*a*]porphyrin-18-yl]propanoato(3-)- κN^{21} , κN^{22} , κN^{23} , κN^{24}]palladate(1-)

Hydrogen (SP-4-2)-[(3*S*,4*S*,13*R*,14*R*,21*R*)-9-acetyl-14-ethyl-13,14-dihydro-21-(methoxycarbonyl)-4,8,13,18-tetramethyl-20-oxo-3-phorbinepropanoato(3-)- κN^{23} , κN^{24} , κN^{25} , κN^{26}]palladate(1-)

Pd-BPheid
WST-09
TOOKAD



C35 H36 N4 O6 Pd; Mol wt: 715.1114

ACTION – Photosensitizer for photodynamic therapy (PDT) proven to completely cure mice bearing human prostate cancer cells within 28-40 days. Compound was also effective and safe in a model of prostate cancer in dogs. A phase I/II clinical study is currently in progress in patients with prostate cancer.

SOURCE – Yeda.

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3. Chen, Q. *Tookad (WST09) mediated photodynamic therapy as an alternative modality in treatment of prostate cancer*. Hong Kong Int PDT Conf (Dec 7-10, Hong Kong) 2001, Abst.
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5. Weersink, R.A. et al. *Determination of the peak absorption wavelength and disaggregation kinetics of TOOKAD in vivo using dynamic, spatially resolved diffuse reflectance spectroscopy in a rabbit model*. Proc SPIE 2002, 4613: 135.
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*Identified compound **291143** Drug Data Rep 2000, 022(10): 0941.

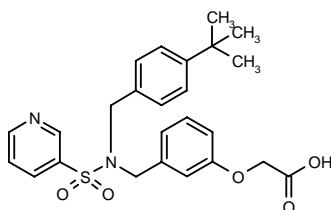
METABOLIC DRUGS

TREATMENT OF BONE DISEASES

CP-533536

320026

2-[3-[N-(4-*tert*-Butylbenzyl)-N-(pyridin-3-ylsulfonyl)amino-methyl]phenoxy]acetic acid



C25 H28 N2 O5 S: Mol wt: 468.5712

ACTION – Potent and highly selective nonprostanoid prostaglandin EP₂ agonist (EC₅₀ = 0.3 nM for increasing cAMP levels in cells expressing rat EP₂ receptors) with high affinity and selectivity for rat EP₂ receptors over rat EP₄ receptors (IC₅₀ = 50 and > 3200 nM, respectively). Compound (3-10 mg/kg) was shown to stimulate bone formation and improve fracture healing in rat models; it was also seen to improve bone healing in dogs at 10 mg/kg. Potentially useful for the treatment of bone diseases.

SOURCE – Pfizer.

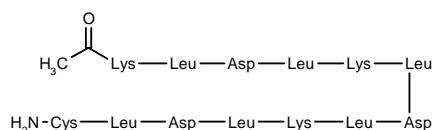
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KLD-12

322781

N²-Acetyl-L-lysyl-L-leucyl-L-aspartyl-L-leucyl-L-lysyl-L-leucyl-L-aspartyl-L-leucyl-L-lysyl-L-leucyl-L-aspartyl-L-leucyl-L-cysteinamide



C71 H127 N17 O20 S; Mol wt: 1570.9490

ACTION – Self-assembling peptide hydrogel scaffold for cartilage repair able to maintain differentiated chondrocytes and to stimulate the synthesis and accumulation of a mechanically functional cartilage-like extracellular matrix in 3D cell culture. Potentially useful for repairing cartilage defects resulting from traumatic injury or degenerative diseases.

SOURCE – Massachusetts Institute of Technology, Cambridge, MA (US).

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2. Bourre, L. et al. *Indirect detection of photosensitizer ex vivo*. J Photochem Photobiol B Biol 2002, 67(1): 23.
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4. Qun, C. et al. *WST09 (TOOKAD) mediated photodynamic therapy as an alternative modality in the treatment of prostate cancer*. Proc SPIE 2002, 4612: 29.
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*Identified compound **291143** Drug Data Rep 2000, 022(10): 0941.

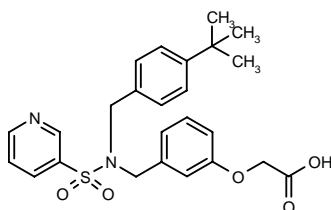
METABOLIC DRUGS

TREATMENT OF BONE DISEASES

CP-533536

320026

2-[3-[N-(4-*tert*-Butylbenzyl)-N-(pyridin-3-ylsulfonyl)amino-methyl]phenoxy]acetic acid



C25 H28 N2 O5 S: Mol wt: 468.5712

ACTION – Potent and highly selective nonprostanoid prostaglandin EP₂ agonist (EC₅₀ = 0.3 nM for increasing cAMP levels in cells expressing rat EP₂ receptors) with high affinity and selectivity for rat EP₂ receptors over rat EP₄ receptors (IC₅₀ = 50 and > 3200 nM, respectively). Compound (3-10 mg/kg) was shown to stimulate bone formation and improve fracture healing in rat models; it was also seen to improve bone healing in dogs at 10 mg/kg. Potentially useful for the treatment of bone diseases.

SOURCE – Pfizer.

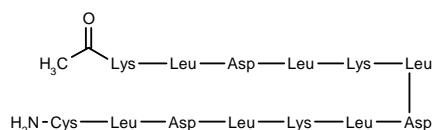
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KLD-12

322781

N²-Acetyl-L-lysyl-L-leucyl-L-aspartyl-L-leucyl-L-lysyl-L-leucyl-L-aspartyl-L-leucyl-L-lysyl-L-leucyl-L-aspartyl-L-leucyl-L-cysteinamide



C71 H127 N17 O20 S; Mol wt: 1570.9490

ACTION – Self-assembling peptide hydrogel scaffold for cartilage repair able to maintain differentiated chondrocytes and to stimulate the synthesis and accumulation of a mechanically functional cartilage-like extracellular matrix in 3D cell culture. Potentially useful for repairing cartilage defects resulting from traumatic injury or degenerative diseases.

SOURCE – Massachusetts Institute of Technology, Cambridge, MA (US).

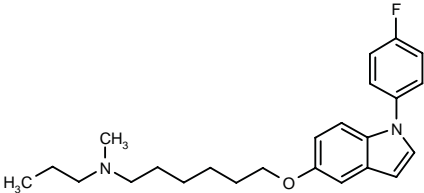
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TREATMENT OF LIPOPROTEIN DISORDERS

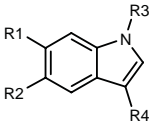
322412

N-[6-[1-(4-Fluorophenyl)-1*H*-indol-5-yloxy]hexyl]-*N*-methyl-*N*-propylamine



C24 H31 F N2 O; Mol wt: 382.5199

ACTION – An inhibitor of 2,3-epoxysqualene–lanosterol cyclase (lanosterol synthase) considered to have potential for the treatment of lipoprotein disorders including hypercholesterolemia, hyperlipidemia, arteriosclerosis, vascular diseases, mycoses, parasite infections, gallstones, cancer, impaired glucose tolerance and diabetes. Other exemplified indole derivatives include the following:



Compound	R1	R2	R3	R4	Formula
322413	H	O(CH2)4N(Et)2	4-Br-PhCH2	H	C ₂₃ H ₂₉ BrN ₂ O
322414	H	allyl-N(Me)(CH2)3	4-F-Ph	H	C ₂₁ H ₂₃ FN ₂
322415	H	(CH2)5N(Me)CH2CH2OH	4-Et-Ph	H	C ₂₄ H ₃₂ N ₂ O
322416	H	1-azetidiny-(CH2)4O	4-Br-Ph	H	C ₂₁ H ₂₃ BrN ₂ O
322417	H	allyl-N(Me)(CH2)3-ethynyl	4-CF3-Ph	Me	C ₂₅ H ₂₅ F ₃ N ₂
322718	H	EtN(CH2CH2OH)CH2-ethynyl	4-F-Ph	H	C ₂₁ H ₂₁ FN ₂ O
322419	F	EtN(CH2CH2OH)(CH2)3-ethynyl	4-F-Ph	H	C ₂₃ H ₂₄ F ₂ N ₂ O
322420	H	4,5-dihydro-2-thiazolyl-N(Me)(CH2)4O	4-F-Ph	H	C ₂₂ H ₂₄ FN ₃ OS

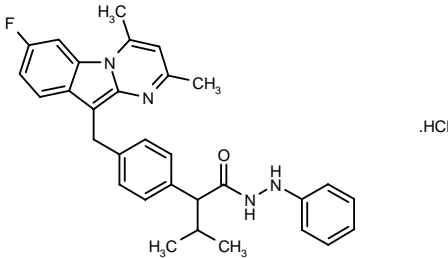
SOURCE – Roche.

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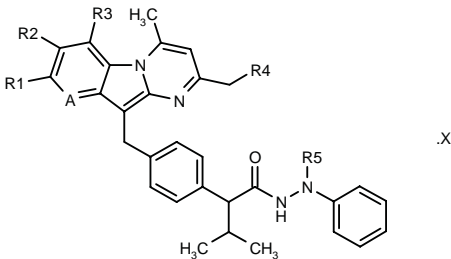
322532

2-[4-(7-Fluoro-2,4-dimethylpyrimido[1,2-*a*]indol-10-ylmethyl)phenyl]-3-methyl-*N*'-phenylbutyrohydrazide hydrochloride

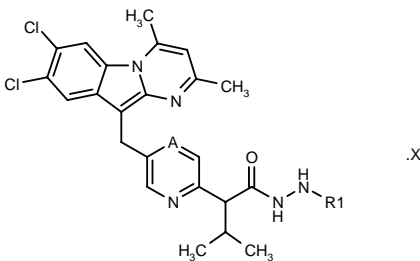


C31 H31 F N4 O . HCl; Mol wt: 531.0718

ACTION – Apolipoprotein B (apo B) secretion inhibitor, potentially useful for the treatment of hyperlipidemia, arteriosclerosis, obesity and pancreatitis. Other exemplified hydrazide derivatives are:



Compound	R1	R2	R3	R4	R5	A	X	Formula
322534	H	Ac	H	H	H	CH	HCl	C ₃₃ H ₃₄ N ₄ O ₂ .HCl
322536	Me	Me	H	H	H	CH		C ₃₃ H ₃₆ N ₄ O
322537	-OCH2O-		H	H	H	CH		C ₃₂ H ₃₂ N ₄ O ₃
322538	Cl	H	Cl	H	Me	CH		C ₃₂ H ₃₂ Cl ₂ N ₄ O
322539	Cl	H	H	H	H	N		C ₃₀ H ₃₀ ClN ₅ O
322544	H	H	H	OH	H	CH		C ₃₁ H ₃₂ N ₄ O ₂



Compound	R1	A	X	Formula
322535	Ph	N	HCl	C ₂₉ H ₂₈ Cl ₂ N ₆ O.HCl
322540	2-Pyr	CH		C ₂₉ H ₂₈ Cl ₂ N ₆ O

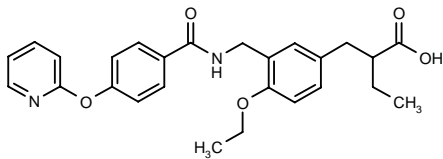
SOURCE – Yamanouchi.

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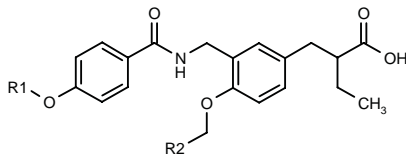
322690

2-[4-Ethoxy-3-[4-(pyridin-2-yloxy)benzamidomethyl]-benzyl]butyric acid

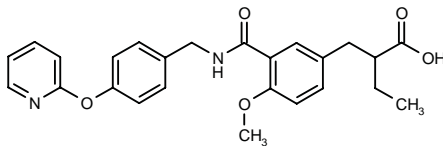


C26 H28 N2 O5; Mol wt: 448.5162

ACTION – Peroxisome proliferator-activated receptor (PPAR) agonist with EC₅₀ values of 0.044, 0.41 and 0.19 μM, respectively, at PPARα, PPARγ and PPARδ receptors expressed in CHO cells. Potentially useful for the treatment of metabolic diseases including hyperlipidemia, arteriosclerosis, diabetes and obesity. Other exemplified compounds are:



Compound	R1	R2	Isomer	Formula
322692	3-Pyr	H		C ₂₅ H ₂₆ N ₂ O ₅
322695	2-Pyr	Me	(+)	C ₂₆ H ₂₈ N ₂ O ₅
322697	2-Pyr	Me	(-)	C ₂₆ H ₂₈ N ₂ O ₅



322691: C25 H26 N2 O5

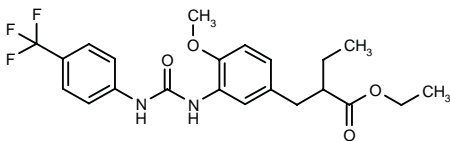
SOURCE – Kyorin.

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1. Miyachi, H. and Murakami, K. (Kyorin Pharmaceutical Co., Ltd.) *Substd. carboxylic acid derivs.* WO 0246161.

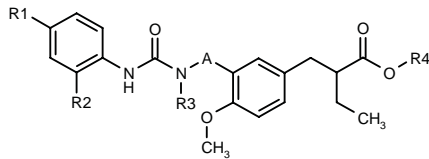
322693

2-[4-Methoxy-3-[3-[4-(trifluoromethyl)phenyl]ureido]-benzyl]butyric acid ethyl ester



C22 H25 F3 N2 O4; Mol wt: 438.4435

ACTION – Peroxisome proliferator-activated receptor (PPAR) agonist, potentially useful for the treatment of metabolic diseases including hyperlipidemia, arterio-sclerosis, diabetes and obesity. Other exemplified compounds are:



Compound	R1	R2	R3	R4	A	Formula
322694	CF3	H	H	H	bond	C ₂₀ H ₂₁ F ₃ N ₂ O ₄
322698	F	F	Pr	Me	-CH2-	C ₂₄ H ₃₀ F ₂ N ₂ O ₄

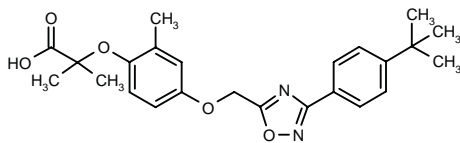
SOURCE – Kyorin.

REFERENCES

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322744

2-[4-[3-(4-*tert*-Butylphenyl)-1,2,4-oxadiazol-5-ylmethoxy]-2-methylphenoxy]-2-methylpropionic acid



C24 H28 N2 O5; Mol wt: 424.4942

ACTION – Peroxisome proliferator-activated receptor PPARα agonist giving an EC₅₀ value of 0.024 μM at PPARα receptors and shown to be selective over PPARδ and PPARγ receptors. Potentially useful for the treatment of dyslipidemia, hyperlipidemia, syndrome X, heart failure, hypercholesterolemia, cardiovascular disease, type 1 and type 2 diabetes, insulin resistance, obesity, anorexia and bulimia.

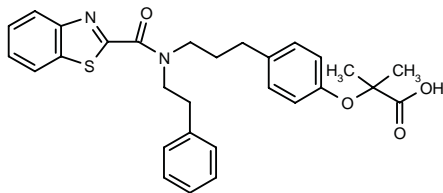
SOURCE – GlaxoSmithKline.

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322856

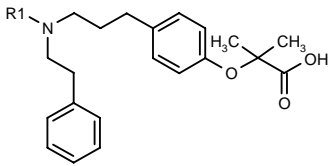
2-[4-[3-[*N*-(Benzothiazol-2-ylcarbonyl)-*N*-(2-phenylethyl)-amino]propyl]phenoxy]-2-methylpropionic acid



C29 H30 N2 O4 S; Mol wt: 502.6320

ACTION – Peroxisome proliferator-activated receptor (PPAR) agonist giving EC₅₀ values of 0.4, 5 and 4.4 μM, respectively, at PPARα, PPARγ and PPARδ receptors expressed in CV-1 cells in a luciferase assay. Potentially useful for the treatment of obesity, syndrome X, hypercholesterolemia, hyperlipidemia, arteriosclerosis, respira-

tory disorders, eating disorders, ischemia, cancer, Alzheimer’s disease, inflammation, osteoporosis, thyrotoxic ophthalmopathy, adrenoleukodystrophy, etc. Other exemplified compounds are:



Compound	R1	Formula
322857	4-i-Pr-2-thiazolyl-CO	C ₂₈ H ₃₄ N ₂ O ₄ S
322861	2-thiazolyl-CO	C ₂₅ H ₂₈ N ₂ O ₄ S
322862	2-benzothiazolyl	C ₂₈ H ₃₀ N ₂ O ₃ S

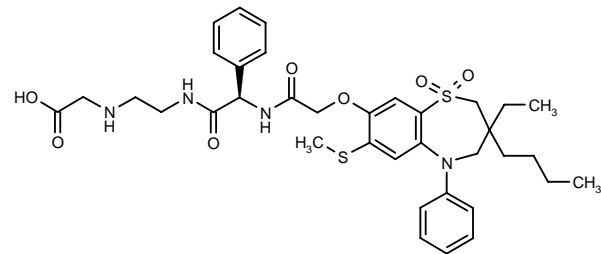
SOURCE – Nippon Chemiphar.

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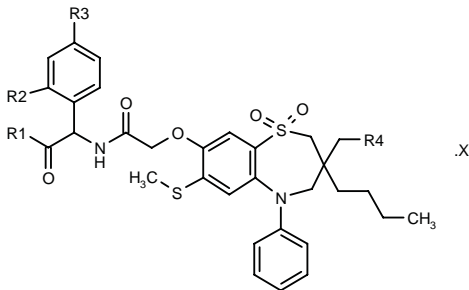
323345

N-[2-[2(*R*)-[2-[3-Butyl-3-ethyl-7-(methylsulfanyl)-1,1-dioxo-5-phenyl-2,3,4,5-tetrahydro-1,5-benzothiazepin-8-yloxy]acetamido]-2-phenylacetamido]ethyl]glycine



C36 H46 N4 O7 S2; Mol wt: 710.9124

ACTION – Agent with the ability to inhibit ileal bile acid transport (IBAT), reportedly useful for the treatment of dyslipidemic conditions, and also atherosclerosis, arteriosclerosis, arrhythmia, hyperthrombotic disorders, vascular or endothelial dysfunction, heart failure, myocardial infarction, angina pectoris, restenosis, stroke, etc. Other exemplified compounds include the following:



Compound	R1	R2	R3	R4	Isomer	X	Formula
323346	-Gly-OH	H	OH	Pr	R		C ₃₆ H ₄₅ N ₃ O ₈ S ₂
323347	NHCH2CH2SO3H	F	H	Pr			C ₃₆ H ₄₆ FN ₃ O ₈ S ₃
323348	-D-His-OH	H	H	Me	R		C ₃₈ H ₄₅ N ₅ O ₇ S ₂
323349	NHCH2PO(OEt)Me	H	H	Me	R		C ₃₆ H ₄₈ N ₃ O ₇ PS ₂
323350	-Gly-OH	H	H	Pr	R		C ₃₆ H ₄₅ N ₃ O ₇ S ₂
323351	NHCH2CH2SO3 ⁻	H	H	Pr	R	NH ₄ ⁺	C ₃₆ H ₄₇ N ₃ O ₈ S ₃ NH ₃

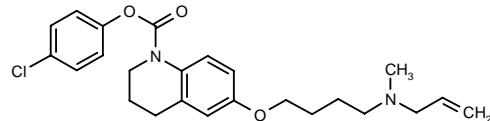
SOURCE – AstraZeneca.

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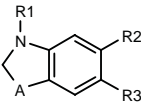
323531

6-[4-(*N*-Allyl-*N*-methylamino)butoxy]-1,2,3,4-tetrahydroquinoline-1-carboxylic acid 4-chlorophenyl ester



C24 H29 Cl N2 O3; Mol wt: 428.9571

ACTION – 2,3-Epoxysqualene–lanosterol cyclase (lanosterol synthase) inhibitor, expected to be useful for the treatment of hypercholesterolemia, hyperlipidemia, arteriosclerosis, vascular diseases, mycoses, parasitic infections, gallstones, cancer, impaired glucose tolerance and diabetes. Other exemplified compounds are:



Compound	R1	R2	R3	A	Formula
323532	CO2Et	H	allyl-N(Me)CH2-CH=CHCH2O	-(CH2)2-	C ₂₀ H ₂₈ N ₂ O ₃
323533	t-BuOCO	H	allyl-N(Me)CH2-CH=CHCH2O	-CH2-	C ₂₁ H ₃₀ N ₂ O ₃
323534	4-F-PhOCS	H	allyl-N(Me)(CH2)4O	-CH2-	C ₂₃ H ₂₇ FN ₂ O ₂ S
323535	2,4-(F)2-Ph-NHCO	H	allyl-N(Me)(CH2)4O	-CH2-	C ₂₃ H ₂₇ F ₂ N ₃ O ₂
323536	4-Br-PhCO	H	allyl-N(Me)(CH2)4O	-CH2-	C ₂₃ H ₂₇ BrN ₂ O ₂
323537	4-F-PhOCS	H	allyl-N(Me)(CH2)5	-CH2-	C ₂₄ H ₂₉ FN ₂ OS
323538	4-Me-PhSO2	F	EtN(CH2CH2OH)-(CH2)3-ethynyl	-CH2-	C ₂₄ H ₂₉ FN ₂ O ₃ S
323539	4-Me-PhSO2	F	(CH2)5N(Me)-CH2CH2OH	-CH2-	C ₂₃ H ₃₁ FN ₂ O ₃ S

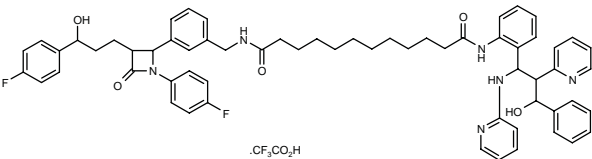
SOURCE – Roche.

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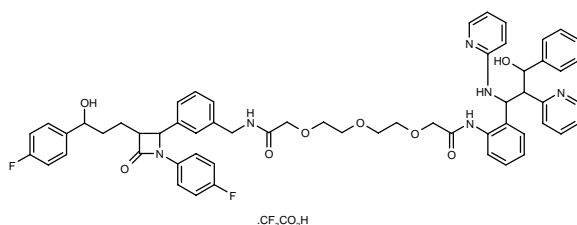
323575

*N*¹-[3-[1-(4-Fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl]benzyl]-*N*¹²-[2-[3-hydroxy-3-phenyl-1-(pyridin-2-ylamino)-2-(2-pyridyl)-propyl]phenyl]dodecanediamide trifluoroacetate

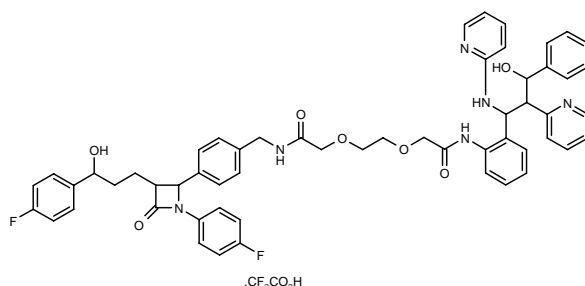


C62 H66 F2 N6 O5 . C2 H F3 O2; Mol wt: 1127.2580

ACTION – Hypolipidemic activity found to decrease liver cholesterol levels following administration to mice with an ED₅₀ value of 0.03 mg/animal. Potentially useful for the treatment of hyperlipidemia, hypercholesterolemia, arteriosclerosis and insulin resistance. Other exemplified azetidinone derivatives are:



323576: C58 H58 F2 N6 O8 . C2 H F3 O2



323577: C56 H54 F2 N6 O7 . C2 H F3 O2

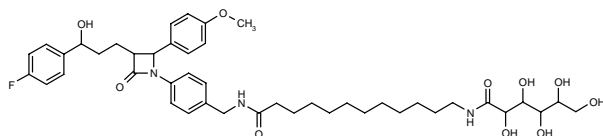
SOURCE – Aventis Pharma.

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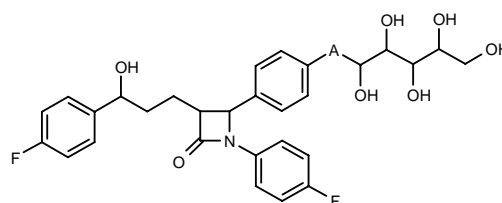
323579

N-[4-[3-[3-(4-Fluorophenyl)-3-hydroxypropyl]-2-(4-methoxyphenyl)-4-oxoazetidin-1-yl]benzyl]-12-(2,3,4,5,6-pentahydroxyhexanamido)dodecanamide

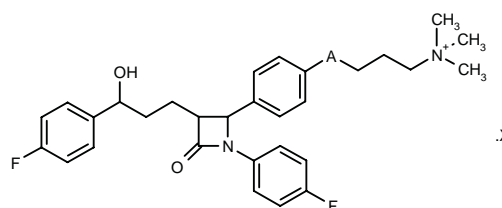


C44 H60 F N3 O10; Mol wt: 809.9670

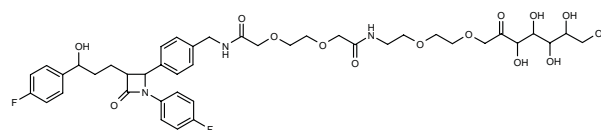
ACTION – Hypolipidemic agent found to decrease liver cholesterol levels following administration to mice with an ED₅₀ value of 0.003 mg/animal. Potentially useful for the treatment of hyperlipidemia, hypercholesterolemia, arteriosclerosis and insulin resistance. Other exemplified azetidinone derivatives are:



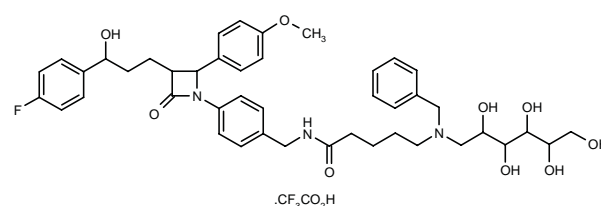
Compound	A	Formula
323580	-CH ₂ NHCO-	C ₃₁ H ₃₄ F ₂ N ₂ O ₈
323587	-O(CH ₂) ₄ NH(Me)CH ₂ -	C ₃₅ H ₄₄ F ₂ N ₂ O ₈
323588	-(OCH ₂ CH ₂) ₃ N(Me)CH ₂ -	C ₃₇ H ₄₈ F ₂ N ₂ O ₁₀



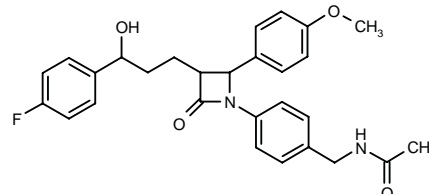
Compound	A	X	Formula
323582	-CH ₂ NHCO-	CF ₃ CO ₂ -	C ₃₄ H ₃₈ F ₉ N ₂ O ₅
323585	-CH ₂ NHCOCH(9-fluorenyl)- -CH ₂ OCONH)CH ₂ -	Cl-	C ₄₉ H ₅₃ ClF ₂ N ₄ O ₅
323586	-OCH ₂ CH ₂ -	Br-	C ₃₂ H ₃₉ BrF ₂ N ₂ O ₃



323581: C42 H53 F2 N3 O14



323583: C44 H54 F N3 O9 . C2 H F3 O2



323584: C28 H29 F N2 O4

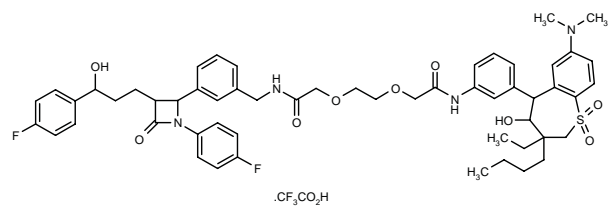
SOURCE – Aventis Pharma.

REFERENCES

1. Glombik, H. et al. (Aventis Pharma Deutschland GmbH) *Novel 1,2-diphenyl-azetidinones, method for producing the same, medicaments containing said cpds., and the use thereof for treating disorders of the lipid metabolism.* WO 0250027.

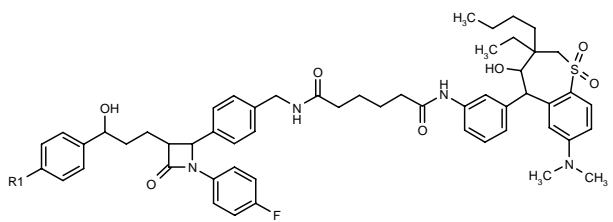
323591

2-[2-[N-[3-[3-Butyl-7-(dimethylamino)-3-ethyl-4-hydroxy-1,1-dioxo-2,3,4,5-tetrahydro-1-benzothiepin-5-yl]phenyl]-carbamoyl-methoxy]ethoxy]-N-[3-[1-(4-fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl]benzyl]acetamide trifluoroacetate

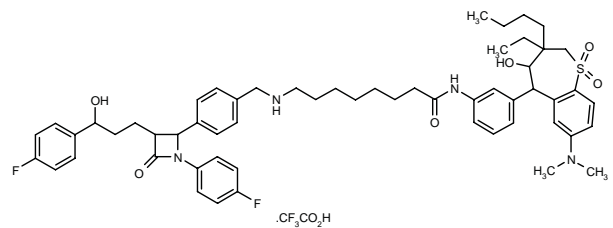


C55 H64 F2 N4 O9 S . C2 H F3 O2; Mol wt: 1109.2140

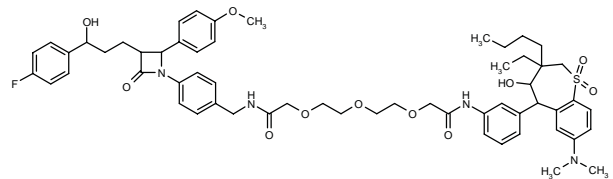
ACTION – Hypolipidemic agent found to decrease liver cholesterol levels following administration to mice with an ED₅₀ value of 0.003 mg/animal. Potentially useful for the treatment of hyperlipidemia, hypercholesterolemia, arteriosclerosis and insulin resistance. Other exemplified azetidinone derivatives are:



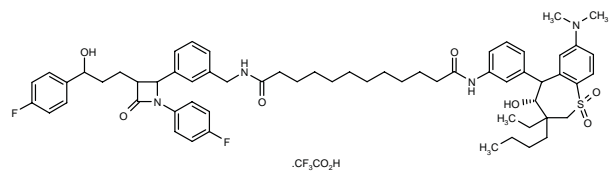
Compound	R1	Formula
323592	H	C ₅₅ H ₆₅ FN ₄ O ₇ S
323593	F	C ₅₅ H ₆₄ F ₂ N ₄ O ₇ S



323595: C57 H70 F2 N4 O6 S . C2 H F3 O2



323597:C58 H71 F N4 O11 S



323642: C61 H76 F2 N4 O7 S . C2 H F3 O2

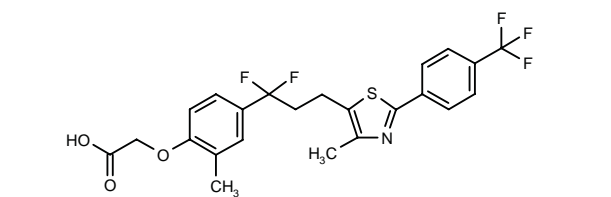
SOURCE – Aventis Pharma.

REFERENCES

1. Glombik, H. et al. (Aventis Pharma Deutschland GmbH) *Diphenyl azetidinone derivs., method for the production thereof, medicaments containing these cpds., and their use.* WO 0250068.

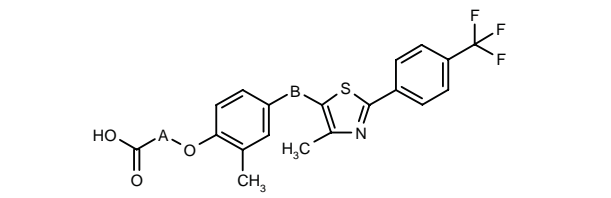
323600

2-[4-[1,1-Difluoro-3-[4-methyl-2-[4-(trifluoromethyl)-phenyl]thiazol-5-yl]propyl]-2-methylphenoxy]acetic acid



C23 H20 F5 N O3 S; Mol wt: 485.4710

ACTION – Peroxisome proliferator-activated receptor PPARδ agonist with potential for the treatment of dyslipidemia and hyperlipidemia, syndrome X, heart failure, hypercholesterolemia, cardiovascular disease, type 1 and type 2 diabetes, insulin resistance, obesity, anorexia, bulimia and inflammation. Other exemplified compounds are:



Compound	A	B	Formula
323601	-CH2-	-(CH2)3-	C ₂₃ H ₂₂ F ₃ NO ₃ S
323602	-CH2-	-CHFCH2-	C ₂₂ H ₁₉ F ₄ NO ₃ S
323604	-CH2-	-CF2CHF-	C ₂₂ H ₁₇ F ₆ NO ₃ S
323606	-CH2-	-CF2CF2-	C ₂₂ H ₁₆ F ₇ NO ₃ S
323609	-(CH2)3-	-(CH2)2-	C ₂₄ H ₂₄ F ₃ NO ₃ S
323610	-(CH2)4-	-(CH2)2-	C ₂₅ H ₂₆ F ₃ NO ₃ S
323611	-CH2-	-(CH2)2-	C ₂₂ H ₂₀ F ₃ NO ₃ S

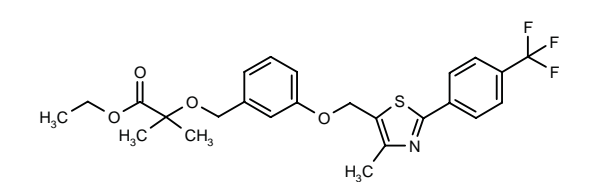
SOURCE – GlaxoSmithKline.

REFERENCES

1. Beswick, P.J. et al. (GlaxoSmithKline plc) *Thia- and oxazoles and their use as PPARs activators.* WO 0250048.

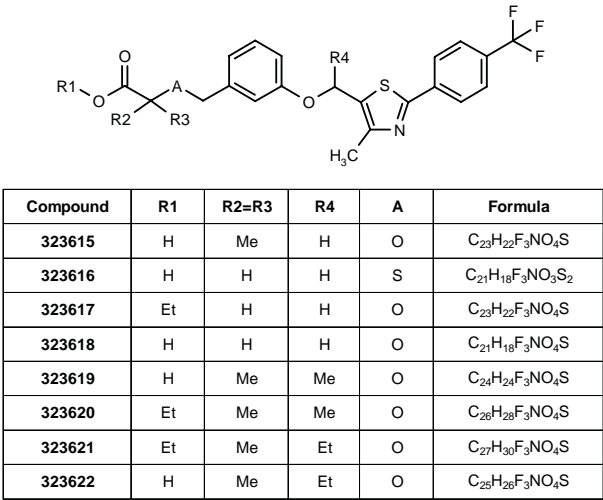
323614

2-Methyl-2-[3-[4-methyl-2-[4-(trifluoromethyl)-phenyl]thiazol-5-ylmethoxy]benzyloxy]propionic acid ethyl ester



C25 H26 F3 N O4 S; Mol wt: 493.5434

ACTION – Peroxisome proliferator-activated receptor PPAR α agonist expected to be useful for the treatment of dyslipidemia and hyperlipidemia, syndrome X, heart failure, hypercholesterolemia, cardiovascular disease, type 1 and type 2 diabetes, insulin resistance, obesity, anorexia, bulimia and inflammation. Other exemplified compounds are:



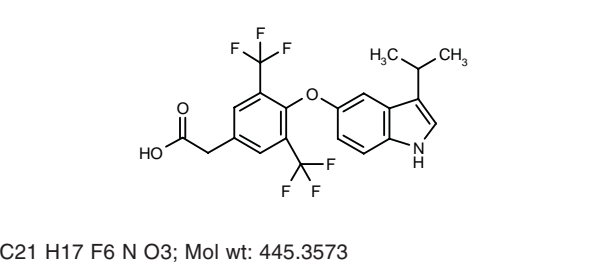
SOURCE – GlaxoSmithKline.

REFERENCES

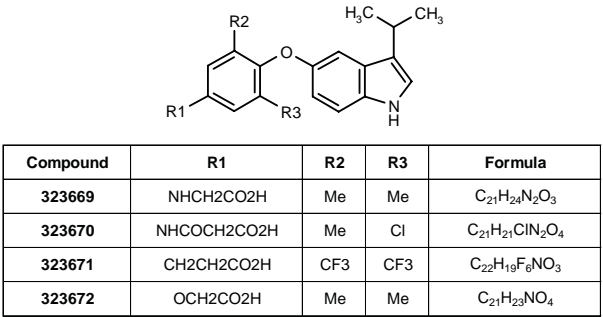
1. Sierra, M.L. (GlaxoSmithKline plc) *Substd. oxazoles and thiazoles as hPPAR α agonists*. WO 0250047.

323668

2-[4-(3-Isopropyl-1*H*-indol-5-yloxy)-3,5-bis(trifluoromethyl)phenyl]acetic acid



ACTION – Thyroid receptor ligand with thyroid hormone-like activity, inducing luciferase activity in HepG2 cells transfected with the luciferase gene under the control of a thyroid hormone-regulated promoter (EC₅₀ = 0.5 nM). Potentially useful for the treatment of arteriosclerosis and hypercholesterolemia. Other exemplified indole derivatives are:



SOURCE – Bayer.

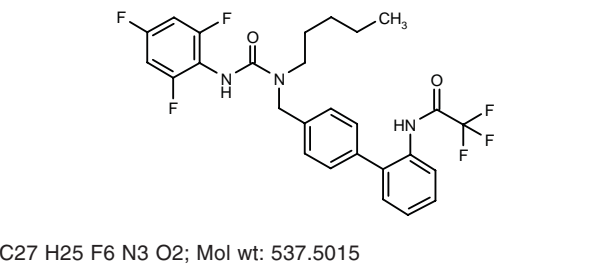
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1. Haning, H. et al. (Bayer AG) *Indole derivs. as ligands of thyroid receptors*. WO 0251805.

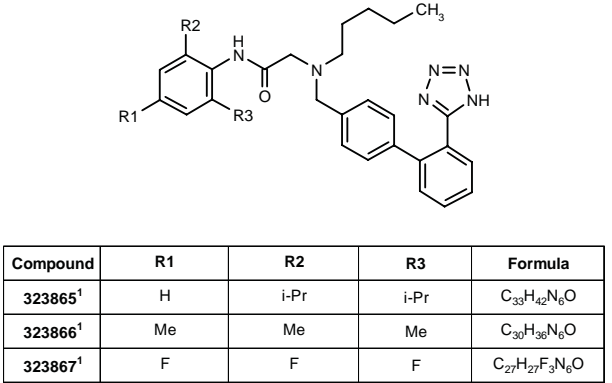
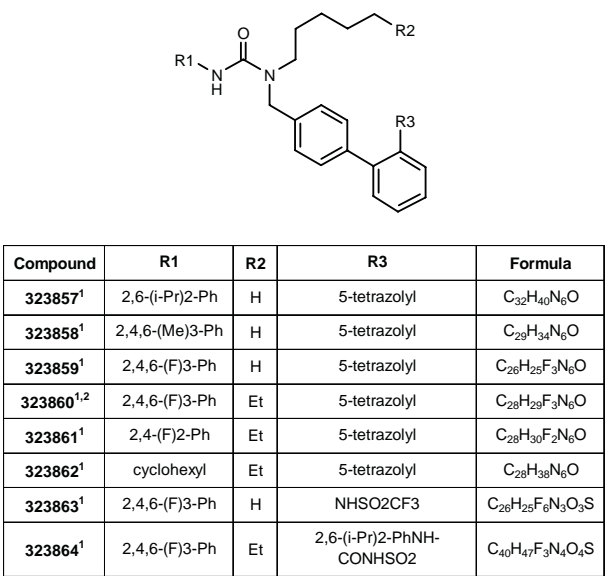
323856¹

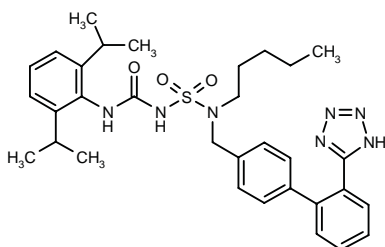
2,2,2-Trifluoro-*N*-[4'-[1-pentyl-3-(2,4,6-trifluorophenyl)-ureidomethyl]biphenyl-2-yl]acetamide

N-Pentyl-*N*-[2'-(2,2,2-trifluoroacetamido)biphenyl-4-ylmethyl]-*N*'-(2,4,6-trifluorophenyl)urea



ACTION – ACAT inhibitor (pIC₅₀ = 6.57) with potential in the treatment of hypercholesterolemia and atherosclerosis. Other exemplified biphenyl derivatives are:





323868¹: C32 H41 N7 O3 S

SOURCE – Pola Chemical.

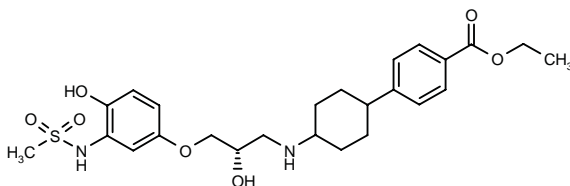
REFERENCES

1. Namiki, T. et al. (Pola Chemical Industries Inc.) *Biphenyl derivs.* WO 0251799.
2. Namiki, P. et al. (Pola Chemical Industries Inc.) *Urea derivs.* JP 2002201127.

TREATMENT OF OBESITY AND NUTRITIONAL DISORDERS

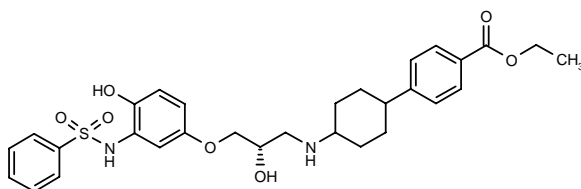
322274

4-[4-[2(S)-Hydroxy-3-[4-hydroxy-3-(methylsulfonamido)-phenoxy]propylamino]cyclohexyl]benzoic acid ethyl ester



C25 H34 N2 O7 S; Mol wt: 506.6166

ACTION – β_3 -Adrenoceptor agonist, potentially useful for the treatment of obesity, diabetes, wound healing and irritable bowel syndrome, and also as a tocolytic agent. Another specifically claimed compound is:



322275: C30 H36 N2 O7 S

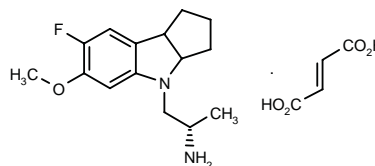
SOURCE – Sanofi-Synthélabo.

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1. Bovy, P.R. et al. (Sanofi-Synthélabo) *Cyclohexyl(alkyl)-propanolamines, preparation method and pharmaceutical compsns. containing same.* FR 2817257, WO 0244139.

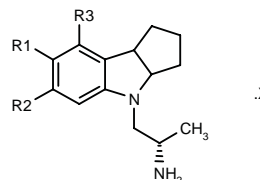
322276

1-(7-Fluoro-6-methoxy-1,2,3,3a,4,8b-hexahydro-cyclopenta[b]indol-4-yl)propan-2(S)-amine fumarate



C15 H21 F N2 O . C4 H4 O4; Mol wt: 380.4135

ACTION – 5-HT_{2C} receptor agonist that gave a K_i of 88 nM at 5-HT_{2C} receptors in radioligand binding assays and exhibited 6- and 13-fold selectivity over 5-HT_{2B} and 5-HT_{2A} receptor subtypes, respectively. In *in vitro* functional assays, compound activated 5-HT_{2C} receptors expressed in CHO cells with an EC₅₀ of 391 nM, while showing no activity at 5-HT_{2A} receptors. Potentially useful for the treatment of obesity, as well as brain and spinal cord trauma, stroke, neurodegenerative diseases, encephalitis, meningitis, thrombosis, dysfunctions of gastrointestinal motility and diabetes, among other 5-HT_{2C}-mediated disorders. Other exemplified indoline derivatives are:



Compound	R1	R2	R3	Isomer	X	Formula
322277	H	Cl	H	3aS,8bS	HCl	C ₁₄ H ₁₉ ClN ₂ .HCl
322278	F	Cl	H	A	fumarate	C ₁₄ H ₁₈ ClFN ₂ .C ₄ H ₄ O ₄
322280	F	H	OMe		fumarate	C ₁₅ H ₂₁ FN ₂ O.C ₄ H ₄ O ₄

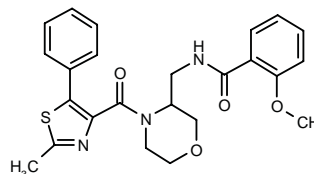
SOURCES – Roche; Vernalis.

REFERENCES

1. Bentley, J.M. et al. (F. Hoffmann-La Roche AG;Vernalis Research Ltd.) *Indoline derivs. and their use as 5-HT₂ receptor ligands.* WO 0244152.

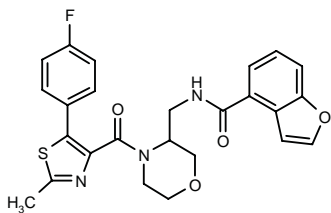
322294

2-Methoxy-N-[4-(2-methyl-5-phenylthiazol-4-ylcarbonyl)-morpholin-3-ylmethyl]benzamide



C24 H25 N3 O4 S; Mol wt: 451.5445

ACTION – Orexin receptor, particularly orexin-1 receptor, antagonist, potentially useful for the treatment of obesity including that associated with type 2 diabetes, and also sleep disorders and ischemic or hemorrhagic stroke. Another exemplified morphine derivative is:



322295: C25 H22 F N3 O4 S

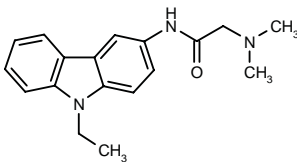
SOURCE – GlaxoSmithKline.

REFERENCES

1. Branch, C.L. et al. (GlaxoSmithKline plc) *Morpholine derivs. as antagonists of orexin receptors*. WO 0244172.

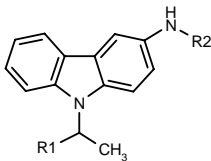
322497

2-(Dimethylamino)-*N*-(9-ethyl-9*H*-carbazol-3-yl)acetamide



C18 H21 N3 O; Mol wt: 295.3839

ACTION – Neuropeptide Y (NPY) Y₅ receptor antagonist potentially useful for the treatment of obesity. Other specifically claimed carbazole derivatives include the following:



Compound	R1	R2	Formula
322498	H	COCH2CH2N(Me)2	C ₁₉ H ₂₃ N ₃ O
322499	H	COCH2NHCH2Ph	C ₂₃ H ₂₃ N ₃ O
322501	H	COCH2CH2Br	C ₁₇ H ₁₇ BrN ₂ O
322502	H	4-F-PhCH2NHCH2CO	C ₂₃ H ₂₂ FN ₃ O
322503	H	4-(1-Pip-CH2)-PhOCH2CH2CO	C ₂₉ H ₃₃ N ₃ O ₂
322504	Me	Ac	C ₁₇ H ₁₈ N ₂ O
322506	H	4-Cl-PhCH2NHCH2CO	C ₂₃ H ₂₂ ClN ₃ O
322507	H	SO2Me	C ₁₅ H ₁₆ N ₂ O ₂ S

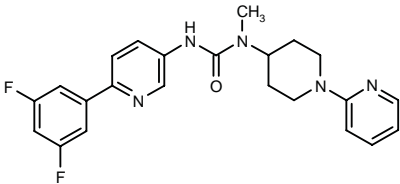
SOURCE – Pfizer.

REFERENCES

1. Elliott, R.L. et al. (Pfizer Inc.) *Carbazole neuropeptide Y5 antagonists*. US 6399631.

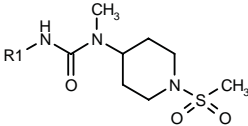
323425

N-[6-(3,5-Difluorophenyl)pyridin-3-yl]-*N'*-methyl-*N'*-[1-(2-pyridyl)piperidin-4-yl]urea

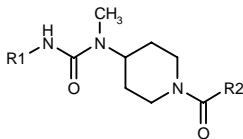


C23 H23 F2 N5 O; Mol wt: 423.4647

ACTION – Neuropeptide Y (NPY) Y₅ receptor antagonist expected to be useful for the treatment of obesity and related disorders such as type 2 diabetes, insulin resistance, hyperlipidemia and hypertension. Other exemplified urea derivatives are:



Compound	R1	Formula
323426	6-[3,5-(F)2-Ph]-3-Pyr	C ₁₉ H ₂₂ F ₂ N ₄ O ₃ S
323428	5-[3,5-(F)2-Ph]-1-oxido-2-Pyr	C ₁₉ H ₂₂ F ₂ N ₄ O ₄ S
323429	5-(3-F-Ph)-2-thienyl	C ₁₈ H ₂₂ FN ₃ O ₃ S ₂
323431	2-[3,5-(F)2-Ph]-5-pyrimidinyl	C ₁₈ H ₂₁ F ₂ N ₅ O ₃ S
323433	6-(3-F-Ph)-3-pyridazinyl	C ₁₈ H ₂₂ FN ₅ O ₃ S



Compound	R1	R2	Formula
323427	5-[3,5-(F)2]-2-Pyr	Me	C ₂₀ H ₂₂ F ₂ N ₄ O ₂
323430	5-(3-F-Ph)-1,3,4-thiadiazol-2-yl	NHMe	C ₁₇ H ₂₁ FN ₆ O ₂ S
323432	2-[3,5-(F)2-Ph]-5-thiazolyl	Me	C ₁₈ H ₂₀ F ₂ N ₄ O ₂ S

SOURCE – Schering-Plough.

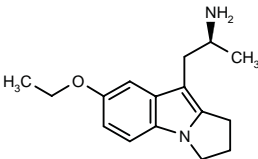
REFERENCES

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323649

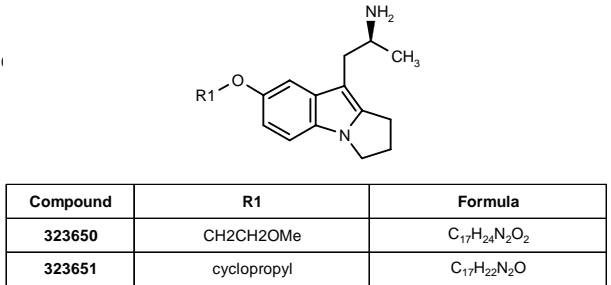
1-(7-Ethoxy-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-9-yl)propyl-2(*S*)-amine

2-(7-Ethoxy-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-9-yl)-1(*S*)-methylethylamine



C16 H22 N2 O; Mol wt: 258.3628

ACTION – Modulator of 5-HT₂ receptors, particularly 5-HT_{2C} receptors, giving K_i values of 11, 830 and 410 nM, respectively, at 5-HT_{2C}, 5-HT_{2B} and 5-HT_{2A} receptors in radioligand binding assays. In functional assays, it displayed agonist activity at 5-HT_{2C} receptors expressed in CHO cells (EC₅₀ = 4 nM). This compound also demonstrated *in vivo* activity in different animal models of obesity following oral administration. Potentially useful for the treatment of eating disorders, obesity and diabetes. Further applications include CNS disorders, cardiovascular disorders, gastrointestinal disorders and sleep apnea. Other exemplified indole derivatives are:



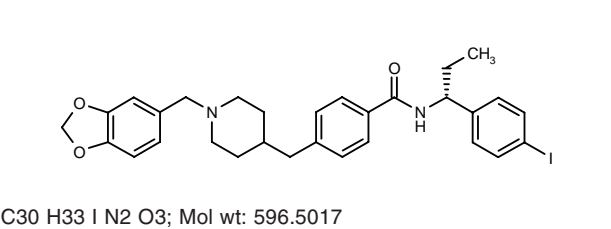
SOURCES – Roche; Vernalis.

REFERENCES

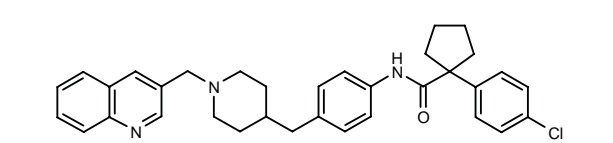
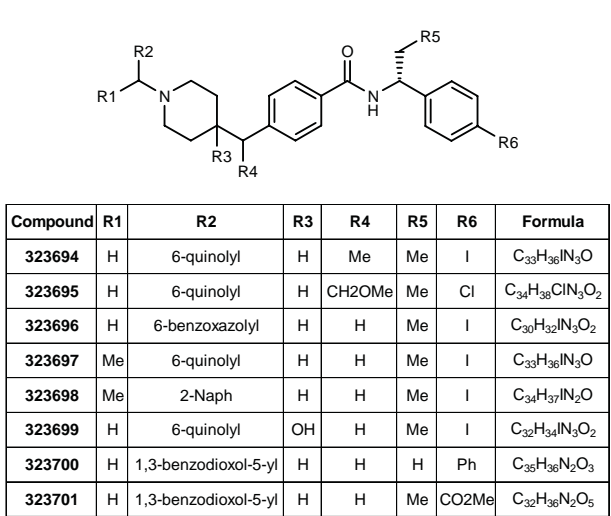
1. Bentley, J.M. et al. (F. Hoffmann-La Roche AG;Vernalis Research Ltd.) *Indole derivs. and their use as 5-HT_{2B} and 5-HT_{2C} receptor ligands.* WO 0251844.

323692

4-[1-(1,3-Benzodioxol-5-ylmethyl)piperidin-4-ylmethyl]-N-[1(R)-(4-iodophenyl)propyl]benzamide



ACTION – Melanin-concentrating hormone (MCH) antagonist for the treatment of eating disorders such as obesity and diabetes. Other exemplified piperidine derivatives are:



323693: C34 H36 Cl N3 O

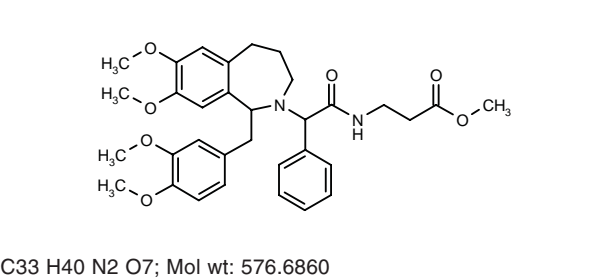
SOURCE – Schering-Plough.

REFERENCES

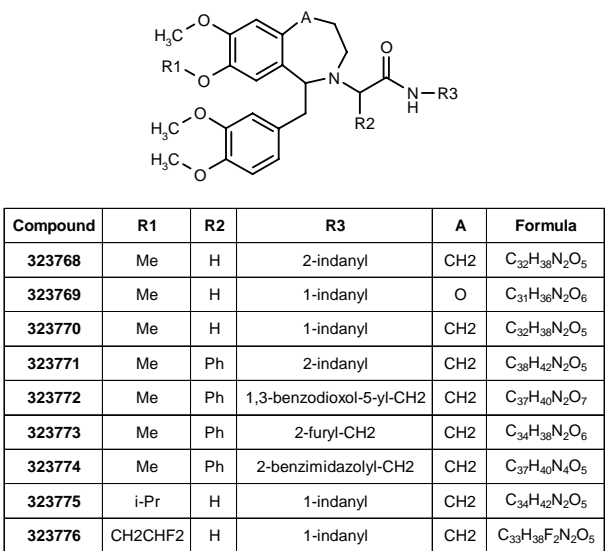
1. McKittrick, B.A. et al. (Schering Corp.) *Piperidine MCH antagonists and their use in the treatment of obesity.* WO 0251809.

323765

3-[2-[1-(3,4-Dimethoxybenzyl)-7,8-dimethoxy-2,3,4,5-tetrahydro-1 H-2-benzazepin-2-yl]-2-phenylacetamido]-propionic acid methyl ester



ACTION – Selective orexin OX1 receptor antagonist that gave IC₅₀ values of 41and 9192 nM in cells expressing OX1 and OX2 receptors, respectively. Potentially useful for the treatment of conditions associated with orexin, particularly obesity and sleep disorders. Other exemplified benzazepines are:



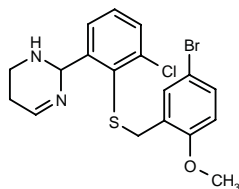
SOURCE – Actelion.

REFERENCES

1. Aissaoui, H. et al. (Actelion Ltd.) *Novel benzazepines and related heterocyclic derivs. which are useful as orexin receptor antagonists.* WO 0251232, WO 0251838.

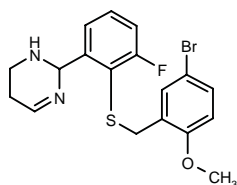
323847

2-[2-(5-Bromo-2-methoxybenzylsulfanyl)-3-chlorophenyl]-1,2,5,6-tetrahydropyrimidine



C18 H18 Br Cl N2 O S; Mol wt: 425.7762

ACTION – Melanocortin MC₄ receptor antagonist with nanomolar affinity for MC₄ receptors ($K_i = \text{nM}$), potentially useful for the treatment of wasting disorders such as cachexia and anorexia. Another related compound is:



323848: C18 H18 Br F N2 O S

SOURCE – Millennium.

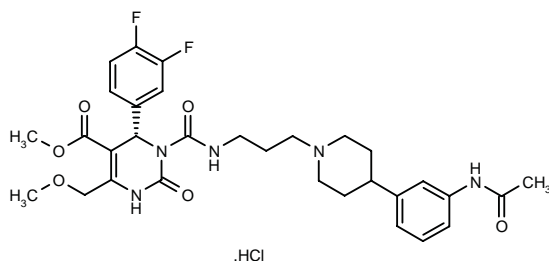
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- Maguire, M.P. et al. (Millennium Pharmaceuticals, Inc.) *Melanocortin-4 receptor binding cpds. and methods of use thereof*. EP 1204645, WO 0110842.
- Vos, T.J. et al. *Identification and chemical optimization of small molecule MC4 receptor antagonists*. 224th ACS Natl Meet (Aug 18-22, Boston) 2002, Abst MEDI 338.

SNAP-7941*

316172

(+)-3-[N-[3-[4-(3-Acetamidophenyl)piperidin-1-yl]propyl]carbamoyl]-4(S)-(3,4-difluorophenyl)-6-(methoxymethyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester hydrochloride



C31 H37 F2 N5 O6 . HCl; Mol wt: 650.1192

ACTION – Melanin-concentrating hormone MCH1 receptor antagonist ($\text{pA}_2 = 9.24$, $K_b = 0.57 \text{ nM}$ for antagonizing MCH-stimulated inositol phosphate turnover in COS-7 cells expressing human MCH1 receptors) with subnanomolar affinity for MCH1 receptors ($K_d = 0.18 \text{ nM}$) and > 1,000-fold selectivity over human MCH2, 5-HT_{2C}, galanin and neuropeptide Y (NPY) receptors. In rats, compound (10 mg/kg i.p.) inhibited the increase in food intake induced by centrally administered MCH and produced a 26% decrease in weight gain compared to controls when given b.i.d. for 7 days. It also reduced the

consumption of palatable food in rats by 13, 41 and 59%, respectively, at doses of 3, 10 and 30 mg/kg i.p. Chronic treatment (10 mg/kg b.i.d. i.p. for 4 weeks) in a rat model of diet-induced obesity produced a significant decrease in body weight (26%) and food consumption, with a profile different from D-fenfluramine. Compound was also active in animal models of depression such as the rat forced swimming test, the rat social interaction test and the guinea pig maternal separation vocalization test, where it demonstrated efficacy following single oral or i.p. doses of 3-30 mg/kg. Potentially useful for the treatment of obesity, as well as depression and anxiety.

SOURCE – Synaptic.

REFERENCES

- Lagu, B. et al. (Synaptic Pharmaceutical Corp.) *Selective melanin concentrating hormone-1 (MCH1) receptor antagonists and uses thereof*. WO 0206245.
- Blackburn, T.P. et al. *Anorectic, antidepressant, and anxiolytic effects of a MCH1 receptor antagonist*. Pharmacologist 2002, 44(2, Suppl. 1): Abst 104.7.
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- Forray, C. et al. *Discovery of SNAP7941: A selective, high-affinity antagonist for MCH1 receptors*. Pharmacologist 2002, 44(2, Suppl. 1): Abst 104.6.
- Marzabadi, M.R. et al. *Discovery of SNAP 7941 and analogs as high affinity MCH-1 antagonists*. 224th ACS Natl Meet (Aug 18-22, Boston) 2002, Abst MEDI 340.

*Identified compound **316172** Drug Data Rep 2002, 024(04): 0389.

TREATMENT OF POISONING, DRUG ABUSE AND DEPENDENCY

1H scAb

323078

scAb fragment of the genetically engineered mouse antibody 1H against the protective antigen (PA) subunit of the toxin produced by Bacillus anthracis

ACTION – High-affinity toxin-neutralizing antibody against the protective antigen (PA) subunit of the toxin produced by *Bacillus anthracis*. The antibody competes with the cellular receptor for PA and has an equilibrium dissociation constant of 0.26 nM. In *B. anthrax* toxin-challenged rats, the antibody (at 5 nmol) completely protected animals against intoxication over 5 h.

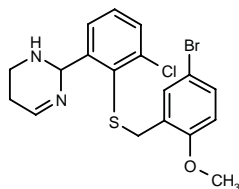
SOURCES – National Institutes of Health, Bethesda, MD (US); University of Texas System, Austin, TX (US).

REFERENCES

- Maynard, J.A. et al. *Protection against anthrax toxin by recombinant antibody fragments correlates with antigen affinity*. Nat Biotechnol 2002, 20(6): 597.

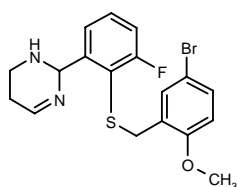
323847

2-[2-(5-Bromo-2-methoxybenzylsulfanyl)-3-chlorophenyl]-1,2,5,6-tetrahydropyrimidine



C18 H18 Br Cl N2 O S; Mol wt: 425.7762

ACTION – Melanocortin MC₄ receptor antagonist with nanomolar affinity for MC₄ receptors (K_i = nM), potentially useful for the treatment of wasting disorders such as cachexia and anorexia. Another related compound is:



323848: C18 H18 Br F N2 O S

SOURCE – Millennium.

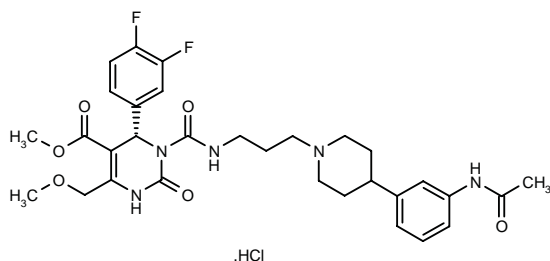
REFERENCES

- Maguire, M.P. et al. (Millennium Pharmaceuticals, Inc.) *Melanocortin-4 receptor binding cpds. and methods of use thereof*. EP 1204645, WO 0110842.
- Vos, T.J. et al. *Identification and chemical optimization of small molecule MC4 receptor antagonists*. 224th ACS Natl Meet (Aug 18-22, Boston) 2002, Abst MEDI 338.

SNAP-7941*

316172

(+)-3-[N-[3-[4-(3-Acetamidophenyl)piperidin-1-yl]propyl]carbamoyl]-4(S)-(3,4-difluorophenyl)-6-(methoxymethyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester hydrochloride



C31 H37 F2 N5 O6 . HCl; Mol wt: 650.1192

ACTION – Melanin-concentrating hormone MCH1 receptor antagonist (pA_2 = 9.24, K_b = 0.57 nM for antagonizing MCH-stimulated inositol phosphate turnover in COS-7 cells expressing human MCH1 receptors) with subnanomolar affinity for MCH1 receptors (K_d = 0.18 nM) and > 1,000-fold selectivity over human MCH2, 5-HT_{2C}, galanin and neuropeptide Y (NPY) receptors. In rats, compound (10 mg/kg i.p.) inhibited the increase in food intake induced by centrally administered MCH and produced a 26% decrease in weight gain compared to controls when given b.i.d. for 7 days. It also reduced the

consumption of palatable food in rats by 13, 41 and 59%, respectively, at doses of 3, 10 and 30 mg/kg i.p. Chronic treatment (10 mg/kg b.i.d. i.p. for 4 weeks) in a rat model of diet-induced obesity produced a significant decrease in body weight (26%) and food consumption, with a profile different from D-fenfluramine. Compound was also active in animal models of depression such as the rat forced swimming test, the rat social interaction test and the guinea pig maternal separation vocalization test, where it demonstrated efficacy following single oral or i.p. doses of 3-30 mg/kg. Potentially useful for the treatment of obesity, as well as depression and anxiety.

SOURCE – Synaptic.

REFERENCES

- Lagu, B. et al. (Synaptic Pharmaceutical Corp.) *Selective melanin concentrating hormone-1 (MCH1) receptor antagonists and uses thereof*. WO 0206245.
- Blackburn, T.P. et al. *Anorectic, antidepressant, and anxiolytic effects of a MCH1 receptor antagonist*. Pharmacologist 2002, 44(2, Suppl. 1): Abst 104.7.
- Borowsky, B. et al. *Antidepressant, anxiolytic and anorectic effects of a melanin-concentrating hormone-1 receptor antagonist*. Nat Med 2002, 8(8): 825.
- Forray, C. et al. *Discovery of SNAP7941: A selective, high-affinity antagonist for MCH1 receptors*. Pharmacologist 2002, 44(2, Suppl. 1): Abst 104.6.
- Marzabadi, M.R. et al. *Discovery of SNAP 7941 and analogs as high affinity MCH-1 antagonists*. 224th ACS Natl Meet (Aug 18-22, Boston) 2002, Abst MEDI 340.

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SOURCES – National Institutes of Health, Bethesda, MD (US); University of Texas System, Austin, TX (US).

REFERENCES

- Maynard, J.A. et al. *Protection against anthrax toxin by recombinant antibody fragments correlates with antigen affinity*. Nat Biotechnol 2002, 20(6): 597.

DIAGNOSTIC AGENTS

¹¹¹In-DTPA-Aβ(3-40)

322400

[N-[2-[N-[2-[N,N-Bis(carboxymethyl)amino]ethyl]-N-(carboxymethyl)amino]ethyl]-N-(carboxymethyl)glycyl-L-glutamyl-L-phenylalanyl-L-arginyl-L-histidyl-L-aspartyl-L-seryl-glycyl-L-tyrosyl-L-glutamyl-L-valyl-L-histidyl-L-histidyl-L-glutamyl-L-lysyl-L-leucyl-L-valyl-L-phenylalanyl-L-phenylalanyl-L-alanyl-L-glutamyl-L-aspartyl-L-valyl-glycyl-L-seryl-L-asparaginy-L-lysyl-glycyl-L-alanyl-L-isoleucyl-L-isoleucyl-glycyl-L-leucyl-L-methionyl-L-valyl-glycyl-glycyl-L-valyl-L-valinato(3-)indium-111In

C201 H303 In N54 O63 S; Mol wt: 4626.9860

ACTION – Agent for Alzheimer’s disease (AD) imaging, a [¹¹¹In]-labeled β-amyloid (Aβ) derivative able to specifically deposit onto both cerebrovascular and parenchymal Aβ in human AD brain *in vitro*. The radiolabeled compound exhibited high stability in rat whole blood and labeled synthetic Aβ with high specificity *in vitro*. When the radio-labeled compound was administered i.v. to rats, it deposited onto and labeled synthetic Aβ previously implanted in rat muscle tissue, allowing noninvasive detection and imaging.

SOURCES – University of California, Los Angeles, Los Angeles, CA (US); University of Cincinnati, Cincinnati, OH (US); University of Minnesota, Minneapolis, MN (US).

REFERENCES

1. Marshall, J.R. et al. *Noninvasive imaging of peripherally injected Alzheimer’s disease type synthetic A β amyloid in vivo*. *Bioconjugate Chem* 2002, 13(2): 276.

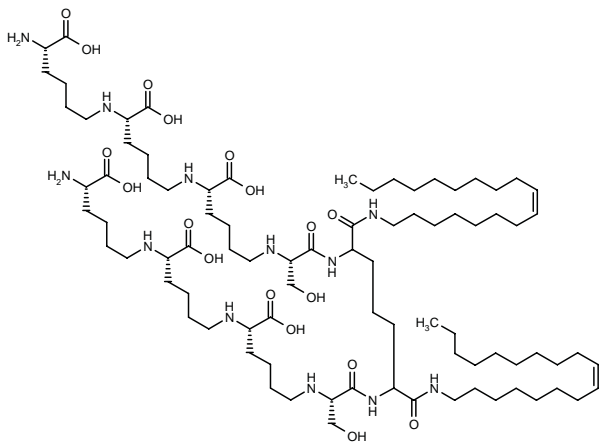
GENOMICS-BASED THERAPIES

GENE DELIVERY SYSTEMS

GSC-112

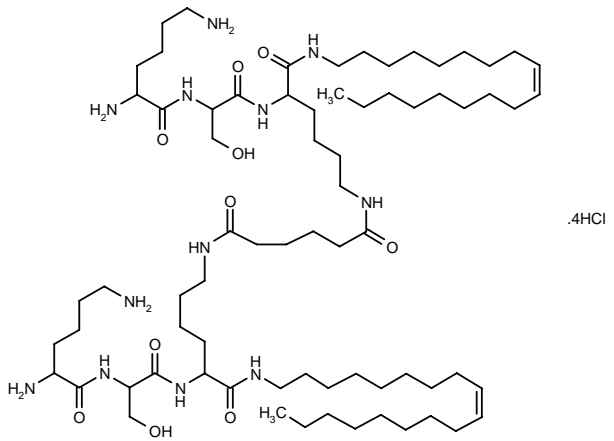
323302

2,6-Bis[N-[5(S)-[5(S)-[5(S)-amino-5-carboxypentylamino]-5-carboxypentylamino]-5-carboxypentyl]-L-serylamino]-N¹,N⁷-bis(8-octadecenyl)heptanediamide



C85 H160 N12 O18; Mol wt: 1638.2650

ACTION – A peptide-substituted symmetric dicarbox-amide derivative for use as a surfactant to facilitate the transfer of polynucleotides and non-nucleotide drugs into cells. GSC-112 was shown to increase the transfection efficiency of luciferase reporter gene plasmids into CHO-K1 cells. Another exemplified compound is:



GSC-150 [323303]: C72 H138 N12 O10 . 4HCl

DIAGNOSTIC AGENTS

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322400

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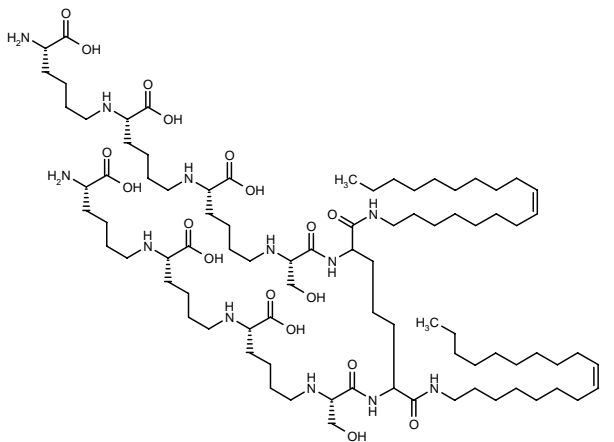
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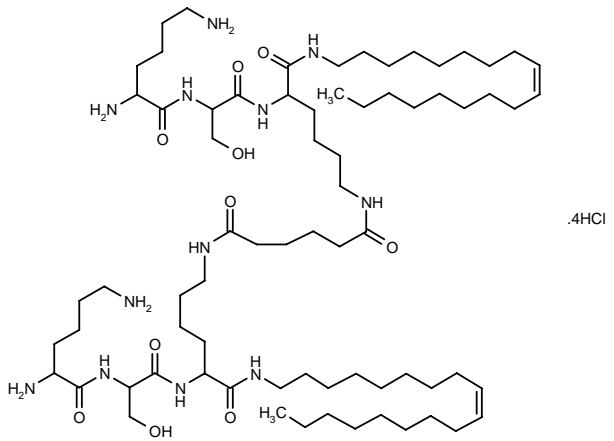
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C85 H160 N12 O18; Mol wt: 1638.2650

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GSC-150 [323303]: C72 H138 N12 O10 . 4HCl

SOURCES – University of Cambridge, Cambridge (GB); GlaxoSmithKline.

REFERENCES

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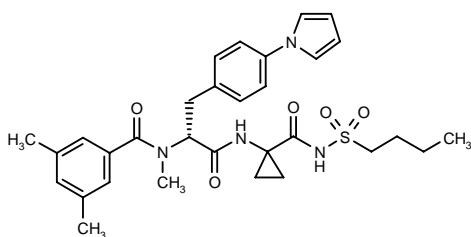
PHARMACOLOGICAL TOOLS

CGS-31398*

243776

N-(Butylsulfonyl)-1-[3-[4-(1-pyrrolyl)phenyl]-2(*R*)-(N,3,5-trimethylbenzamido)propionamido]cyclopropane-1-carboxamide

*N*¹-[1-[*N*-(Butylsulfonyl)carbamoyl]cyclopropyl]-*N*²-(3,5-dimethylbenzoyl)-*N*²-methyl-4-(1*H*-pyrrol-1-yl)-*D*-phenylalaninamide



C31 H38 N4 O5 S; Mol wt: 578.7302

ACTION – Dual endothelin ET_A/ET_B receptor antagonist with high affinity for both human ET_A and ET_B receptors (IC₅₀ = 0.55 and 0.26 nM, respectively) and functional selectivity for ET_B (pK_B > 9 for blockade of sarafotoxin S6c-induced contractions of dog saphenous vein) over ET_A receptors (pK_B = 6.4 for blockade of ET-1-mediated contractions in rat aorta). In anesthetized rats compound potentiated ET-1-induced renal vascular resistance.

SOURCE – Novartis.

REFERENCES

1. Ksander, G.M. et al. (Novartis AG) *N-Aroylamino acid amides as endothelin inhibitors.* EP 0821670, JP 1999505522, WO 9633170.
2. Ksander, G.M. et al. *Dipeptide sulfonamides as endothelin ET_A/ET_B receptor antagonists.* Can J Physiol Pharmacol 2002, 80(5): 464.

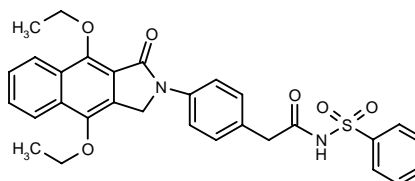
*Identified compound **243776** Drug Data Rep 1997, 019(03): 0231.

GW-627368X

323474

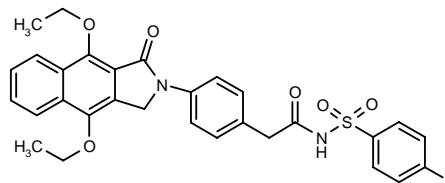
N-[2-[4-(4,9-Diethoxy-1-oxo-2,3-dihydro-1*H*-benzo[*f*]isoindol-2-yl)phenyl]acetyl]benzenesulfonamide

2-[4-(4,9-Diethoxy-1-oxo-2,3-dihydro-1*H*-benzo[*f*]isoindol-2-yl)phenyl]-*N*-(phenylsulfonyl)acetamide



C30 H28 N2 O6 S; Mol wt: 544.6252

ACTION – Potent, competitive prostanoid EP₄ receptor antagonist (pK_b = 9.2) with high binding affinity for EP₄ receptors (pK_i = 7.3) and selectivity over other prostanoid receptors including EP₁, EP₂, EP₃, FP, DP and IP receptors (pK_i < 5.1) and TP receptors (pK_i = 6.9). Compound exhibited good oral pharmacokinetics in rats with a half-life of 3.8 h and a bioavailability of 55%. Potentially useful as a pharmacological tool. Another related compound is:



323473: C30 H27 F N2 O6 S

SOURCE – GlaxoSmithKline.

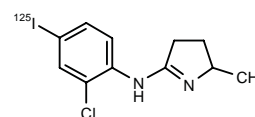
REFERENCES

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2. Giblin, G.M.P. et al. *Novel nonprostanoid prostaglandin EP4 receptor antagonist.* 224th ACS Natl Meet (Aug 18-22, Boston) 2002, Abst MEDI 306.

[¹²⁵I]-LNP-911

322060

N-(2-Chloro-4-[¹²⁵I]-iodophenyl)-2-methyl-3,4-dihydro-2*H*-pyrrol-5-amine



C11 H12 Cl I N2; Mol wt: 332.6828

SOURCES – University of Cambridge, Cambridge (GB); GlaxoSmithKline.

REFERENCES

1. Camilleri, P. et al. (GlaxoSmithKline plc;University of Cambridge) *Novel cpds.* WO 0250100.

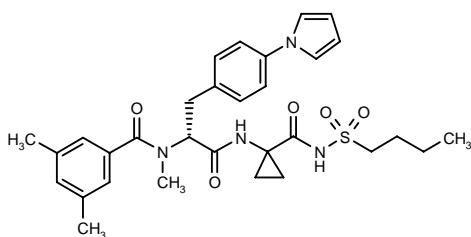
PHARMACOLOGICAL TOOLS

CGS-31398*

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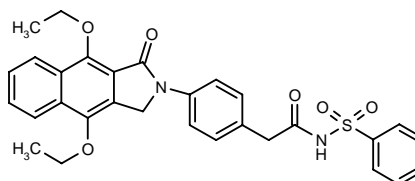
*Identified compound **243776** Drug Data Rep 1997, 019(03): 0231.

GW-627368X

323474

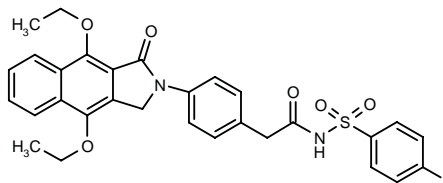
N-[2-[4-(4,9-Diethoxy-1-oxo-2,3-dihydro-1*H*-benzo[*f*]isoindol-2-yl)phenyl]acetyl]benzenesulfonamide

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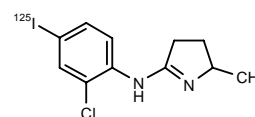
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[¹²⁵I]-LNP-911

322060

N-(2-Chloro-4-[¹²⁵I]-iodophenyl)-2-methyl-3,4-dihydro-2*H*-pyrrol-5-amine



C11 H12 Cl I N2; Mol wt: 332.6828

ACTION – Potent and selective radioligand for imidazoline I₁ receptors. The nonradiolabeled compound exhibited a K_d value of 1.7 nM for imidazoline I₂ receptors. Saturation experiments using the radiolabeled compound showed a single high-affinity binding site in PC-12 cells and high selectivity over imidazoline I₂ receptors and α₂-adrenoceptors.

SOURCE – Université Louis Pasteur, Strasbourg (FR).

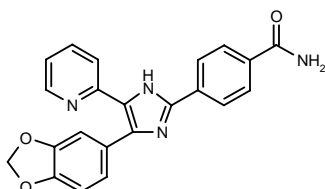
REFERENCES

1. Grenay, H. et al. [¹²⁵I]LNP 911, a high-affinity radioligand selective for I₁ imidazoline receptors. *Pharmacologist* 2002, 44(2, Suppl. 1): Abstr 62.1.

SB-431542

315909

4-[4-(1,3-Benzodioxol-5-yl)-5-(2-pyridyl)-1H-imidazol-2-yl]benzamide



C₂₂ H₁₆ N₄ O₃; Mol wt: 384.3934

ACTION – Potent inhibitor of transforming growth factor β1 (TGF-β1) type I receptors (ALK5; IC₅₀ = 94 nM) shown to selectively inhibit TGF-β1 signaling, as demonstrated by inhibition of TGF-β1-induced fibronectin mRNA formation in A-498 cells (IC₅₀ = 50 nM) and Smad phosphorylation. No effect on ERK, JNK or p38 MAP kinase pathways and no cytotoxicity in A-498 cells was seen. Potentially useful as a pharmacological tool for elucidating the role of TGF-β1 in cellular mechanisms and signaling.

SOURCE – GlaxoSmithKline.

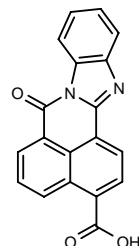
REFERENCES

1. Burgess, J.L. and Callahan, J.F. (GlaxoSmithKline Inc.) *Triarylimidazoles*. EP 1169317, WO 0061576.
2. Callahan, J.F. et al. *Identification of novel inhibitors of the transforming growth factor β1 (TGF-β1) type 1 receptor (ALK5)*. *J Med Chem* 2002, 45(5): 999.
3. Inman, G.J. et al. *SB-431542 is a potent and specific inhibitor of transforming growth factor-β superfamily type I activin receptor-like kinase (ALK) receptors ALK4, ALK5, and ALK7*. *Mol Pharmacol* 2002, 62(1): 65.
4. Laping, N.J. et al. *Inhibition of transforming growth factor (TGF)-β1-induced extracellular matrix with a novel inhibitor of the TGF-β type I receptor kinase activity: SB-431542*. *Mol Pharmacol* 2002, 62(1): 58.

STO-609

323522

7-Oxo-7H-benzimidazo[2,1-a]benzo[de]isoquinoline-3-carboxylic acid



C₁₉ H₁₀ N₂ O₃; Mol wt: 314.2990

ACTION – Selective inhibitor of Ca²⁺/calmodulin-dependent protein kinase kinase (CaM-KK) active against both CaM-KKα and CaM-KKβ isoforms (IC₅₀ = 120 and 40 ng/ml, respectively) and selective over other CaM and protein kinases. Compound inhibited in a concentration-dependent manner the Ca²⁺-induced CaM-KIV activation in transfected HeLa cells, and reduced the endogenous activity of CaM-KK in neuroblastoma SH-SY5Y cells. Potentially useful as a tool for evaluating the physiological role of CaM-KK-mediated pathways.

SOURCE – Sumitomo Pharmaceuticals.

REFERENCES

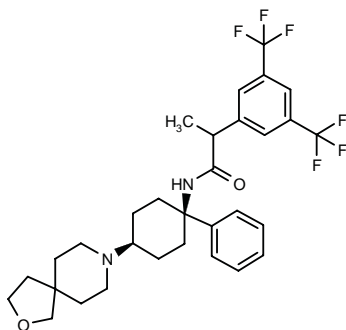
1. Tokumitsu, H. et al. *STO-609, a specific inhibitor of the Ca²⁺/calmodulin-dependent protein kinase kinase*. *J Biol Chem* 2002, 277(18): 15813.

ANALGESIC AND ANESTHETIC
DRUGS

ANALGESIC DRUGS

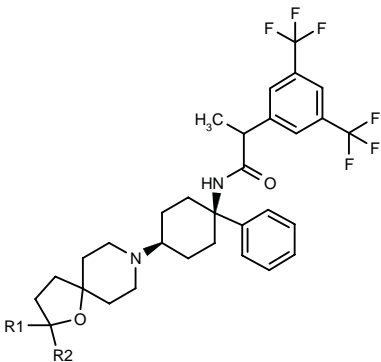
322904

cis-2-[3,5-Bis(trifluoromethyl)phenyl]-*N*-[4-(2-oxa-8-azaspiro[4.5]dec-8-yl)-1-phenylcyclohexyl]propionamide



C₃₁ H₃₆ F₆ N₂ O₂; Mol wt: 582.6254

ACTION – Tachykinin NK₁ receptor antagonist with subnanomolar affinity for human NK₁ receptors (IC₅₀ = 0.34 nM) and high selectivity over potassium channels. Compound exhibited good brain penetration and long-lasting activity after systemic administration, as demonstrated in the foot-tapping test in gerbils (ID₅₀ = 1.1 and 1.6 mg/kg i.v. at 1 and 24 h after dosing, respectively). It was also effective after oral dosing (ID₅₀ = 2.2 mg/kg at 24 h). Claimed for the treatment of pain, inflammation, migraine, emesis, postherpetic neuralgia, depression and anxiety. Other related compounds are:



Compound	R1	R2	Formula
322902	H	H	C ₃₁ H ₃₆ F ₆ N ₂ O ₂
322905	Me	Me	C ₃₃ H ₄₀ F ₆ N ₂ O ₂

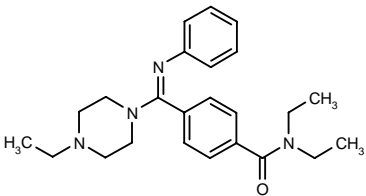
SOURCE – Merck Sharp & Dohme.

REFERENCES

1. Castro Pineiro, J.L. et al. (Merck Sharp & Dohme Ltd.) *Cyclohexane derivs. and their use as therapeutic agents*. WO 0187838.
2. Cooper, L.C. et al. *4,4-Disubstituted cyclohexylamine NK1 receptor antagonists II*. Bioorg Med Chem Lett 2002, 12(13): 1759.

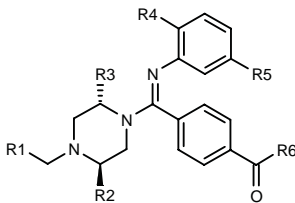
323034

N,N-Diethyl-4-[1-(4-ethylpiperazin-1-yl)-1-(phenylimino)-methyl]benzamide



C₂₄ H₃₂ N₄ O; Mol wt: 392.5438

ACTION – Delta opioid receptor modulator with K_i values of 10 and > 10,000 nM, respectively, at delta and mu opioid receptors in rat brain preparations. Compound inhibited acetylcholine bromide-induced abdominal constriction in mice by 40% after a dose of 150 µmol/kg p.o., demonstrating *in vivo* analgesic activity. Other exemplified benzamidine derivatives are:



Compound	R1	R2=R3	R4	R5	R6	Formula
323035	Me	H	H	Cl	N(Et)2	C ₂₄ H ₃₁ ClN ₄ O
323036	Me	H	H	Br	N(Et)2	C ₂₄ H ₃₁ BrN ₄ O
323037	Me	H	H	Br	N(Pr)2	C ₂₆ H ₃₅ BrN ₄ O
323039	Me	H	Cl	H	N(Et)2	C ₂₄ H ₃₁ ClN ₄ O
323040	Me	H	H	F	N(Pr)2	C ₂₆ H ₃₅ FN ₄ O
323047	Me	H	F	H	N(Et)2	C ₂₄ H ₃₁ FN ₄ O
323048	vinyl	Me	H	H	N(Et)2	C ₂₇ H ₃₆ N ₄ O
323049	vinyl	H	Cl	H	N(Et)2	C ₂₅ H ₃₃ ClN ₄ O
323051	Ph	H	Cl	H	N(Et)2	C ₂₉ H ₃₃ ClN ₄ O
323052	2-thienyl-CH2	H	Cl	H	N(Et)2	C ₂₈ H ₃₃ ClN ₄ OS
323053	Me	H	H	H	OMe	C ₂₁ H ₂₅ N ₃ O ₂
323054	Me	H	H	H	OMe	C ₂₂ H ₂₇ N ₃ O ₃

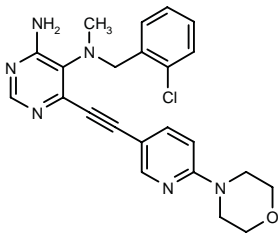
SOURCE – Ortho-McNeil.

REFERENCES

1. Baxter, E.W. et al. (Ortho-McNeil Pharmaceutical, Inc.) *Benzamidine derivs.* WO 0248122.

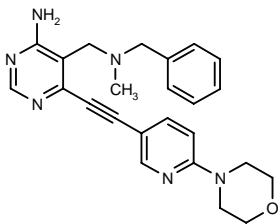
323105

N⁵-(2-Chlorobenzyl)-N⁵-methyl-6-[6-(4-morpholinyl)-pyridin-3-ylethynyl]pyrimidine-4,5-diamine



C23 H23 Cl N6 O; Mol wt: 434.9287

ACTION – Analgesic agent, a potent adenosine kinase inhibitor (IC₅₀ = 15 nM) found to inhibit adenosine phosphorylation in human neuroblastoma IMR-32 cells (IC₅₀ = 100 nM). It showed significant activity in rat models of inflammatory and chemically induced pain, i.e., the formalin test and carrageenan-induced thermal hyperalgesia (ED₅₀ = 10 and 3 μmol/kg i.p., respectively). Another related compound is:



323106: C24 H26 N6 O

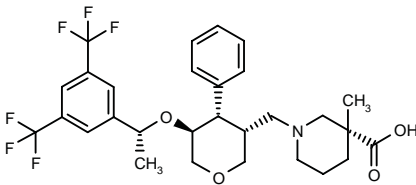
SOURCE – Abbott.

REFERENCES

1. Gomtsyan, A. et al. *Design, synthesis, and structure-activity relationship of 6-alkylpyrimidines as potent adenosine kinase inhibitors.* J Med Chem 2002, 45(17): 3639.

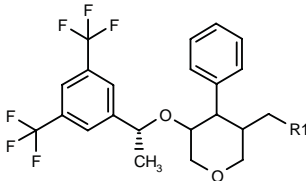
324656

1-[5(S)-[1(R)-[3,5-Bis(trifluoromethyl)phenyl]ethoxy]-4(S)-phenyltetrahydro-2H-pyran-3(R)-ylmethyl]-3-methylpiperidine-3(R)-carboxylic acid



C29 H33 F6 N O4; Mol wt: 573.5707

ACTION – Tachykinin NK₁ receptor antagonist for use in the treatment of pain, inflammation, migraine, emesis, postherpetic neuralgia, depression and anxiety. Other exemplified tetrahydropyran derivatives include the following:



Compound	R1	Isomer	Formula
324657	(R)-3-CO2H-3-Me-1-Pip	3S,4R,5S	C ₂₉ H ₃₃ F ₆ NO ₄
324658	(R)-3-CO2H-3-Me-1-Pip	3R,4S,5R	C ₂₉ H ₃₃ F ₆ NO ₄
324659	(R)-3-CO2H-3-Me-1-Pip	3R,4R,5R	C ₂₉ H ₃₃ F ₆ NO ₄
324660	CN	3S,4R,5R	C ₂₃ H ₂₁ F ₆ NO ₂
324661	2-Me-5-tetrazolyl	3S,4R,5R	C ₂₄ H ₂₄ F ₆ N ₄ O ₂
324662	1-Me-5-tetrazolyl	3S,4R,5R	C ₂₄ H ₂₄ F ₆ N ₄ O ₂
324663	3-oxo-3,4-dihydro-2H-1,2,4-triazol-5-yl	3S,4R,5R	C ₂₄ H ₂₃ F ₆ N ₃ O ₃
324664	1,2,4-triazol-3-yl	3S,4R,5R	C ₂₄ H ₂₃ F ₆ N ₃ O ₂

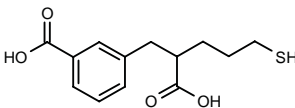
SOURCE – Merck Sharp & Dohme.

REFERENCES

1. Castro Pineiro, J.L. et al. (Merck Sharp & Dohme Ltd.) *Tetrahydropyran derivs. as neurokinin receptor antagonists.* WO 0257250.

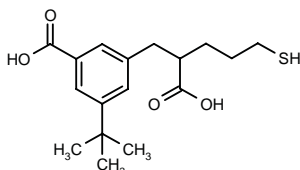
324670

3-(2-Carboxy-5-sulfanylpentyl)benzoic acid



C13 H16 O4 S; Mol wt: 268.3314

ACTION – An inhibitor of *N*-acetylated- γ -linked-acidic dipeptidase (NAALADase) that displayed *in vivo* activity in a rat model of neuropathic pain. Potentially useful for the treatment of glutamate abnormalities, particularly alcohol, nicotine or cocaine abuse, stroke, demyelinating disease, schizophrenia, anxiety, memory impairment and glaucoma, CNS disorders including diabetic neuropathic pain, Parkinson's disease and amyotrophic lateral sclerosis, and also cancer, angiogenesis and TGF- β -related disorders. Another exemplified thiol-based compound is:



324671: C17 H24 O4 S

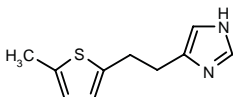
SOURCE – Guilford.

REFERENCES

1. Tsukamoto, T. et al. (Guilford Pharmaceuticals Inc.) *Thiol-based NAALADase inhibitors*. WO 0257222.

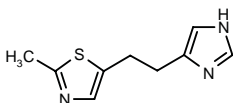
324769

4-[2-(5-Methylthien-2-yl)ethyl]-1*H*-imidazole



C10 H12 N2 S; Mol wt: 192.2848

ACTION – α_2 -Adrenoceptor agonist with a K_i of 1.1 nM at α_{2D} -adrenoceptors in rat cortical preparations. *In vivo*, compound demonstrated oral analgesic activity in the mouse acetylcholine bromide-induced abdominal constriction assay. Another specifically claimed imidazoethylthiophene derivative is:



324958: C9 H11 N3 S

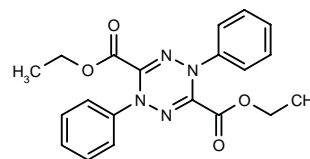
SOURCE – Ortho-McNeil.

REFERENCES

1. Baxter, E.W. and Jetter, M.C. (Ortho-McNeil Pharmaceutical, Inc.) *Imidazoethyl thiophenes*. US 6426356.

325144

1,4-Diphenyl-1,4-dihydro-1,2,4,5-tetraazine-3,6-dicarboxylic acid diethyl ester



C20 H20 N4 O4; Mol wt: 380.4020

ACTION – A representative compound from a series of nitrogen-containing heterocyclic compounds with affinity for cannabinoid CB₂ receptors; its CB₂-agonist activity was demonstrated by its ability to inhibit the production of cAMP in mouse spleen preparations (IC_{50} = 8 nM). Potentially useful for the treatment of pain, glaucoma, epilepsy, nausea associated with cancer chemotherapy, cancer, neurodegenerative diseases, inflammation, motor dysfunction and as a contraceptive.

SOURCE – University of Connecticut, Storrs, CT (US).

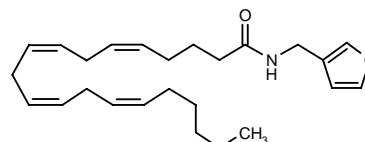
REFERENCES

1. Makriyannis, A. and Deng, H. (University of Connecticut) *Novel cannabimimetic ligands*. WO 0258636.

UCM-707

312662

N-(Furan-3-ylmethyl)-5(*Z*),8(*Z*),11(*Z*),14(*Z*)-icosatetra-enamide



C25 H37 N O2; Mol wt: 383.5723

ACTION – An inhibitor of the anandamide transporter (ANT; IC_{50} = 0.8 μ M in human lymphoma U-937 cells) with little or no affinity for other components of the endogenous cannabinoid system such as fatty acid amide hydrolase (FAAH; IC_{50} = 30 μ M), cannabinoid CB₁ or CB₂ receptors (IC_{50} > 1000 and 67 μ M, respectively) and the vanilloid VR1 receptor (IC_{50} > 5000 μ M). *In vivo*, compound potentiated the hypokinetic and antinociceptive effects of anandamide. Selected as a candidate for further evaluation.

SOURCE – Universidad Complutense de Madrid, Madrid (ES).

REFERENCES

1. Lopez Rodriguez, M.L. et al. (Universidad Complutense de Madrid) *Novel araquidonic acid derivs. with affinity toward the anandamide transporter*. WO 0212167.

2. de Lago, E. et al. *UCM707, a potent and selective inhibitor of endocannabinoid uptake, potentiates hypokinetic and antinociceptive effects of anandamide*. Eur J Pharmacol 2002, 449(1-2): 99.

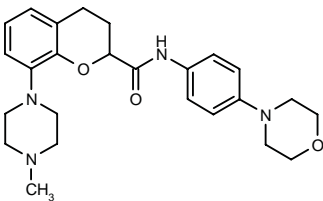
3. López-Rodríguez, M.L. et al. *Design, synthesis and biological evaluation of new endocannabinoid transporter inhibitors*. *Drugs Fut* 2002, 27(Suppl. A): Abst C63.

4. López-Rodríguez, M.L. et al. *Design, synthesis and biological evaluation of novel arachidonic acid derivatives as highly potent and selective endocannabinoid transporter inhibitors*. *J Med Chem* 2001, 44(26): 4505.

ANTIMIGRAINE DRUGS

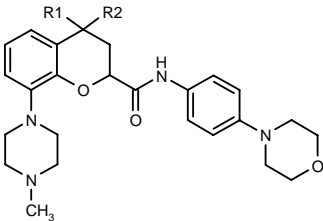
324480

(±)-8-(4-Methylpiperazin-1-yl)-*N*-[4-(4-morpholinyl)-phenyl]-3,4-dihydro-2*H*-1-benzopyran-2-carboxamide



C25 H32 N4 O3; Mol wt: 436.5528

ACTION – Agent with 5-HT_{1B} and/or 5-HT_{1D} receptor-agonist activity, potentially useful for the treatment of migraine. Other 3,4-dihydro-2*H*-1-benzopyran derivatives include the following:



Compound	R1	R2	Isomer	Formula
324482	H	H	(+)	C ₂₅ H ₃₂ N ₄ O ₃
324483	H	H	(-)	C ₂₅ H ₃₂ N ₄ O ₃
324484	-O-		racemic	C ₂₅ H ₃₀ N ₄ O ₄
324485	-O-		isomer A	C ₂₅ H ₃₀ N ₄ O ₄
324486	-O-		isomer B	C ₂₅ H ₃₀ N ₄ O ₄

SOURCE – AstraZeneca.

REFERENCES

1. Chapdelaine, M. et al. (AstraZeneca AB) *Therapeutic chroman cpds*. WO 0255014.

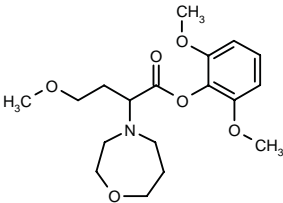
2. Chapdelaine, M. et al. (AstraZeneca AB) *Therapeutic heterocyclic cpds*. WO 0255012.

PSYCHOPHARMACOLOGIC DRUGS

TREATMENT OF SLEEP DISORDERS

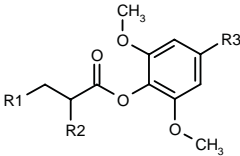
324523

4-Methoxy-2-(perhydro-1,4-oxazepin-4-yl)butyric acid 2,6-dimethoxyphenyl ester



C18 H27 N O6; Mol wt: 353.4123

ACTION – GABA_A receptor modulator with potential as a sedative and analgesic, as well as in the treatment of GABA-mediated disorders such as anxiety, stress, sleep disorders, postpartum depression, premenstrual tension and seizures. The hypnotic potency of this compound was assessed *in vivo* following i.v. administration to mice, where it displayed an HD₅₀ value (dose required to cause a loss of righting reflex of 30 s or more in 50% of mice) of 15 μmol/kg. Other exemplified alanine 2,6-dialkoxyphenyl ester derivatives are:



Compound	R1	R2	R3	Isomer	Formula
324524	CH2OMe	perhydro- -1-azepinyl	H		C ₁₉ H ₂₉ NO ₅
324526	CH2OEt	perhydro- -1-azepinyl	Me		C ₂₁ H ₃₃ NO ₅
324527	4-thiomorpholinyl	4-thiomorpholinyl	H		C ₁₉ H ₂₈ N ₂ O ₄ S ₂
324528	4-morpholinyl	4-thiomorpholinyl	H		C ₁₉ H ₂₈ N ₂ O ₅ S
324529	4-morpholinyl	1-Pip	H		C ₂₀ H ₃₀ N ₂ O ₅
324531	4-thiomorpholinyl	4-morpholinyl	H		C ₁₉ H ₂₈ N ₂ O ₅ S
324533	1,2,5,6-tetra- hydro-1-Pyr	4-thiomorpholinyl	H		C ₂₀ H ₂₈ N ₂ O ₄ S
324536	CH2SMe	perhydro- -1-azepinyl	H		C ₁₉ H ₂₉ NO ₄ S
324537	CH2OMe	perhydro- -1,4-oxazepin-4-yl	H		C ₁₈ H ₂₇ NO ₆
324539	OMe	perhydro- -1,4-oxazepin-4-yl	H	R	C ₁₇ H ₂₅ NO ₆

SOURCE – Akzo Nobel.

REFERENCES

1. Hamilton, N.M. and Bennett, D.J. (Akzo Nobel N.V.) *Alanine 2,6-dialkoxyphenyl ester derivs. as hypnotics*. WO 0257218.

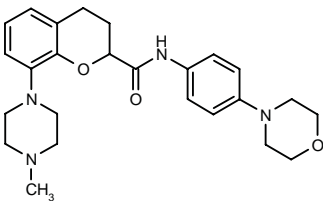
3. López-Rodríguez, M.L. et al. *Design, synthesis and biological evaluation of new endocannabinoid transporter inhibitors*. *Drugs Fut* 2002, 27(Suppl. A): Abst C63.

4. López-Rodríguez, M.L. et al. *Design, synthesis and biological evaluation of novel arachidonic acid derivatives as highly potent and selective endocannabinoid transporter inhibitors*. *J Med Chem* 2001, 44(26): 4505.

ANTIMIGRAINE DRUGS

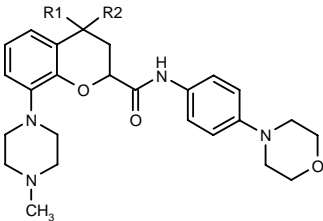
324480

(±)-8-(4-Methylpiperazin-1-yl)-*N*-[4-(4-morpholinyl)-phenyl]-3,4-dihydro-2*H*-1-benzopyran-2-carboxamide



C25 H32 N4 O3; Mol wt: 436.5528

ACTION – Agent with 5-HT_{1B} and/or 5-HT_{1D} receptor-agonist activity, potentially useful for the treatment of migraine. Other 3,4-dihydro-2*H*-1-benzopyran derivatives include the following:



Compound	R1	R2	Isomer	Formula
324482	H	H	(+)	C ₂₅ H ₃₂ N ₄ O ₃
324483	H	H	(-)	C ₂₅ H ₃₂ N ₄ O ₃
324484	-O-		racemic	C ₂₅ H ₃₀ N ₄ O ₄
324485	-O-		isomer A	C ₂₅ H ₃₀ N ₄ O ₄
324486	-O-		isomer B	C ₂₅ H ₃₀ N ₄ O ₄

SOURCE – AstraZeneca.

REFERENCES

1. Chapdelaine, M. et al. (AstraZeneca AB) *Therapeutic chroman cpds*. WO 0255014.

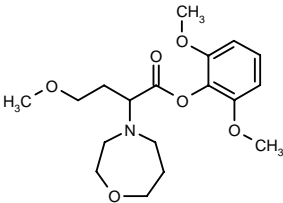
2. Chapdelaine, M. et al. (AstraZeneca AB) *Therapeutic heterocyclic cpds*. WO 0255012.

PSYCHOPHARMACOLOGIC DRUGS

TREATMENT OF SLEEP DISORDERS

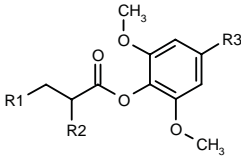
324523

4-Methoxy-2-(perhydro-1,4-oxazepin-4-yl)butyric acid 2,6-dimethoxyphenyl ester



C18 H27 N O6; Mol wt: 353.4123

ACTION – GABA_A receptor modulator with potential as a sedative and analgesic, as well as in the treatment of GABA-mediated disorders such as anxiety, stress, sleep disorders, postpartum depression, premenstrual tension and seizures. The hypnotic potency of this compound was assessed *in vivo* following i.v. administration to mice, where it displayed an HD₅₀ value (dose required to cause a loss of righting reflex of 30 s or more in 50% of mice) of 15 μmol/kg. Other exemplified alanine 2,6-dialkoxyphenyl ester derivatives are:



Compound	R1	R2	R3	Isomer	Formula
324524	CH2OMe	perhydro- -1-azepinyl	H		C ₁₉ H ₂₉ NO ₅
324526	CH2OEt	perhydro- -1-azepinyl	Me		C ₂₁ H ₃₃ NO ₅
324527	4-thiomorpholinyl	4-thiomorpholinyl	H		C ₁₉ H ₂₈ N ₂ O ₄ S ₂
324528	4-morpholinyl	4-thiomorpholinyl	H		C ₁₉ H ₂₈ N ₂ O ₅ S
324529	4-morpholinyl	1-Pip	H		C ₂₀ H ₃₀ N ₂ O ₅
324531	4-thiomorpholinyl	4-morpholinyl	H		C ₁₉ H ₂₈ N ₂ O ₅ S
324533	1,2,5,6-tetra- hydro-1-Pyr	4-thiomorpholinyl	H		C ₂₀ H ₂₈ N ₂ O ₄ S
324536	CH2SMe	perhydro- -1-azepinyl	H		C ₁₉ H ₂₉ NO ₄ S
324537	CH2OMe	perhydro- -1,4-oxazepin-4-yl	H		C ₁₈ H ₂₇ NO ₆
324539	OMe	perhydro- -1,4-oxazepin-4-yl	H	R	C ₁₇ H ₂₅ NO ₆

SOURCE – Akzo Nobel.

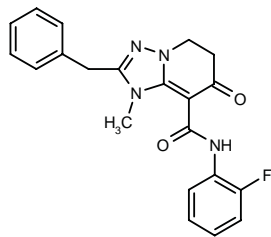
REFERENCES

1. Hamilton, N.M. and Bennett, D.J. (Akzo Nobel N.V.) *Alanine 2,6-dialkoxyphenyl ester derivs. as hypnotics*. WO 0257218.

ANXIOLYTICS

323759

2-Benzyl-*N*-(2-fluorophenyl)-1-methyl-7-oxo-1,5,6,7-tetrahydro[1,2,4]triazolo[1,5-*a*]pyridine-8-carboxamide



C21 H19 F N4 O2; Mol wt: 378.4051

ACTION – GABA_A/benzodiazepine site receptor agonist (*K*_i = 2.5 nM), potentially useful for the treatment of anxiety and sleep disorders.

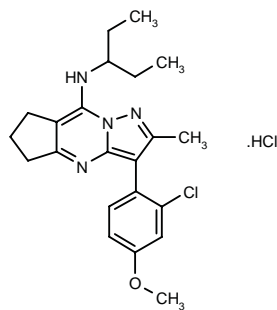
SOURCES – Lilly; Neurogen.

REFERENCES

1. Gustavson, L.M. et al. *Synthesis and evaluation of 5,6-dihydro-8H-[1,2,4]triazolo-[1,5-*a*]pyridin-7-one derivatives, novel GABA_A/benzodiazepine receptor agonists.* 224th ACS Natl Meet (Aug 18-22, Boston) 2002, Abst MEDI 8.

324279

3-(2-Chloro-4-methoxyphenyl)-*N*-(1-ethylpropyl)-2-methyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrazolo[1,5-*a*]pyrimidin-8-amine hydrochloride



C22 H27 Cl N4 O . HCl; Mol wt: 435.3962

ACTION – Corticotropin-releasing factor (CRF) antagonist that demonstrated significant anxiolytic activity in the elevated plus-maze test in rats at oral doses of 3 and 10 mg/kg. Potentially useful for the treatment of depression, anxiety, eating disorders, etc.

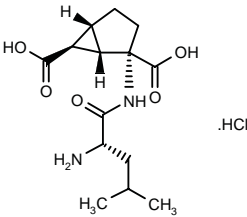
SOURCE – Ono.

REFERENCES

1. Nakai, H. and Kagamiishi, Y. (Ono Pharmaceutical Co., Ltd.) *Tricyclic and heterocyclic deriv. cpds. and drugs containing these cpds. as the active ingredient.* WO 0253565.

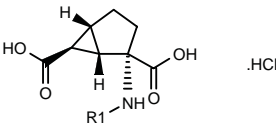
324306

(1*S*,2*S*,5*R*,6*S*)-2-(*L*-Leucylamino)bicyclo[3.1.0]hexane-2,6-dicarboxylic acid hydrochloride



C14 H22 N2 O5 . HCl; Mol wt: 334.7977

ACTION – Synthetic excitatory amino acid prodrug for the treatment of neurological and psychiatric disorders. The compound acts as a prodrug of LY-354740⁺, a known group II metabotropic glutamate receptor (mGluR2/3) agonist that is currently in clinical trials as a potential treatment for anxiety disorders. Other specifically claimed compounds are:



Compound	R1	Formula
324307	H-L-Phe-	C ₁₇ H ₂₀ N ₂ O ₅ .HCl
324308	H-L-Val-	C ₁₃ H ₂₀ N ₂ O ₅ .HCl
324309	H-L-Ile-	C ₁₄ H ₂₂ N ₂ O ₅ .HCl
324310	H-Gly-	C ₁₁ H ₁₄ N ₂ O ₇ .HCl
324312	H-L-Met-	C ₁₃ H ₂₀ N ₂ O ₅ .HCl
324313	H-L-Tyr-	C ₁₇ H ₂₀ N ₂ O ₆ .HCl
324315	H-L-Thr-	C ₁₂ H ₁₈ N ₂ O ₆ .HCl
324316	H-L-Nval-L-Ala-	C ₁₆ H ₂₅ N ₃ O ₆ .HCl
324317	H-L-Ala-L-Ala-	C ₁₄ H ₂₁ N ₃ O ₆ .HCl

SOURCE – Lilly.

REFERENCES

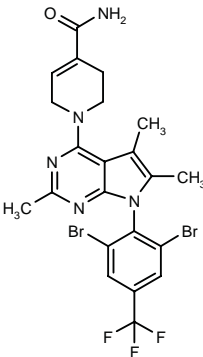
1. Coffey, D.S. et al. (Eli Lilly and Company) *Prodrugs of excitatory amino acids.* WO 0255485.

*Drug Data Rep 1996, 018(09): 0775.

CRA-0316*

294837

1-[7-[2,6-Dibromo-4-(trifluoromethyl)phenyl]-2,5,6-trimethyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl]-1,2,3,6-tetrahydropyridine-4-carboxamide



C22 H20 Br2 F3 N5 O; Mol wt: 587.2360

ACTION – Corticotropin-releasing factor (CRF₁) receptor antagonist with nanomolar affinity for CRF₁ receptors in monkey amygdala (IC₅₀ = 28 nM), high metabolic stability in both rat and human liver microsomes (t_{1/2} = 23 and 28 min, respectively), good brain penetration (ratio brain/plasma = 3.0) and discrete oral bioavailability (25%). Potentially useful for the treatment of anxiety and depression.

SOURCE – Taisho.

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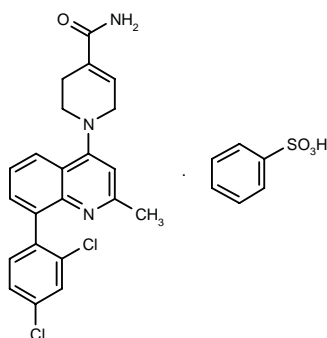
*Identified compound **294837** (see **294834**) Drug Data Rep 2001, 023(02): 0121.

CRA-0450

324072

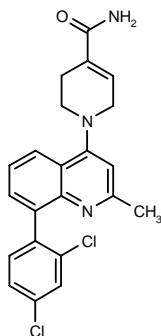
1-[8-(2,4-Dichlorophenyl)-2-methylquinolin-4-yl]-1,2,3,6-tetrahydropyridine-4-carboxamide benzenesulfonate

R-278995



C22 H19 Cl2 N3 O . C6 H6 O3 S; Mol wt: 570.4945

ACTION – Benzenesulfonate salt of **CRA-0390**, a potent corticotropin-releasing factor CRF₁ receptor antagonist (IC₅₀ = 64 nM in monkey amygdala) with improved tissue distribution and pharmacokinetics. Potentially useful for the treatment of anxiety and depression.



CRA-0390* [315529]: C22 H19 Cl2 N3 O

SOURCES – Johnson & Johnson; Taisho.

REFERENCES

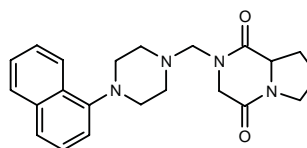
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3. Nakazato, A. et al. *Synthesis, SAR and biological activities of CRH1 receptor: Novel 3- or 4-carbamoyl-1,2,5,6-tetrahydropyridinoquinoline derivative.* 224th ACS Natl Meet (Aug 18-22, Boston) 2002, Abst MEDI 258.

*Identified compound **315529** Drug Data Rep 2002, 024(04): 0302.

CSP-2503

323888

2-[4-(1-Naphthyl)piperazin-1-ylmethyl]perhydropyrrolo-[1,2-a]pyrazine-1,4-dione



C22 H26 N4 O2; Mol wt: 378.4734

ACTION – 5-HT_{1A} receptor agonist with high affinity and selectivity for 5-HT_{1A} receptors (K_i = 6.7 nM) over α₁-adrenoceptors (K_i > 1 μM). It exhibited anxiolytic properties *in vivo*.

SOURCES – Universitat Autònoma de Barcelona, Bellaterra (ES); Universidad Complutense de Madrid, Madrid (ES).

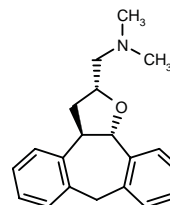
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JNJ-17297709

324333

(2*R**,3*aR**,12*bS**)-*N,N*-Dimethyl-*N*-(3,3*a*,8,12*b*-tetrahydro-2*H*-dibenzo[3,4:6,7]cyclohepta[1,2-*b*]furan-2-ylmethyl)amine



C20 H23 N O; Mol wt: 293.4077

ACTION – Potent 5-HT_{2A/2C} receptor antagonist with high affinity for 5-HT_{2A}, 5-HT_{2C} and histamine H₁ receptors (pIC₅₀ = 7.73, 8.52 and 9.1, respectively). *In vivo*, compound showed potential anxiolytic properties, as demonstrated by activity in the mCPP challenge test in rats.

SOURCE – Janssen.

REFERENCES

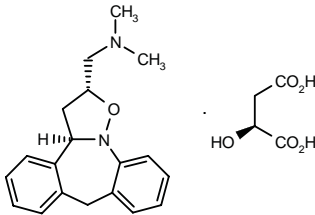
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R-107500

323886

(+)-*N,N*-Dimethyl-*N*-[(2*R*,3*aR*)-2,3,3*a*,8-tetrahydro-dibenzo[*c,f*]isoxazolo[2,3-*a*]azepin-2-ylmethyl]amine L-malate



C19 H22 N2 O . C4 H6 O5; Mol wt: 428.4822

ACTION – Potent central 5-HT_{2A/2C} receptor antagonist with additional peripheral histamine H₁ receptor-antagonist activity and weak central antidopaminergic activity. Selected as a candidate for clinical evaluation as a potential anxiolytic agent.

SOURCE – Janssen.

REFERENCES

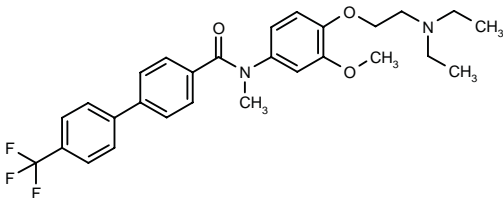
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2. Andrés, J.I. et al. *R107500. A new 5-HT_{2A/2C} antagonist with potential anxiolytic profile.* Drugs Fut 2002, 27(Suppl. A): Abst C41.

SB-568849

324386

N-[4-[2-(Diethylamino)ethoxy]-3-methoxyphenyl]-*N*-methyl-4'-(trifluoromethyl)biphenyl-4-carboxamide



C28 H31 F3 N2 O3; Mol wt: 500.5579

ACTION – Potent and selective antagonist of melanin-concentrating hormone (MCH) with high affinity for the 11CBy receptor (pK_i = 7.7) and > 30-fold selectivity relative to a wide range of monoamine receptors including 5-HT_{2C} receptors. Compound showed good aqueous solubility, good brain penetration and a favorable pharmacokinetic profile with high oral bioavailability (80%) and low clearance (16 ml/min/kg) in rats. It was able to antagonize the effects of MCH on corticotropin-releasing factor (CRF) in rat brain. Potentially useful for the treatment of anxiety, depression and/or eating disorders.

SOURCE – GlaxoSmithKline.

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1. Johnson, C.N. et al. (GlaxoSmithKline plc) *Carboxamide cpds. and their use as antagonists of a human 11CBy receptor.* WO 0210146.

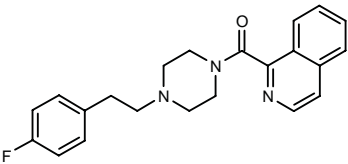
2. Witty, D.R. et al. *Biphenyl carboxamide antagonists of the human melanin-concentrating hormone receptor 11CBy; discovery and SAR.* Drugs Fut 2002, 27(Suppl. A): Abst P537.

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ANTIPSYCHOTIC DRUGS

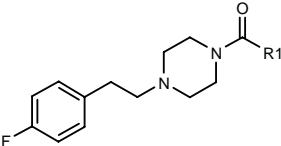
324588

1-[4-[2-(4-Fluorophenyl)ethyl]piperazin-1-yl]-1-(1-isoquinoliny)methanone



C22 H22 F N3 O; Mol wt: 363.4338

ACTION – 5-HT_{2A} receptor antagonist, expected to be useful for the treatment of schizophrenia, as well as depression, memory disorders, Parkinson's disease, amyotrophic lateral sclerosis, Alzheimer's disease, Huntington's disease, eating disorders such as bulimia and anorexia nervosa, premenstrual syndrome and obsessive-compulsive disorder. Other specifically claimed compounds are:



Compound	R1	Formula
324589	2-quinolyl	C ₂₂ H ₂₂ FN ₃ O
324590	8-quinolyl	C ₂₂ H ₂₂ FN ₃ O
324591	3-isoquinoliny	C ₂₂ H ₂₂ FN ₃ O

SOURCE – Merck KGaA.

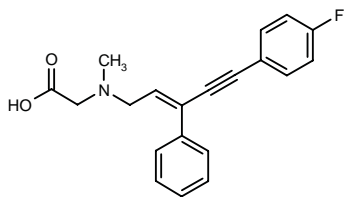
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324856

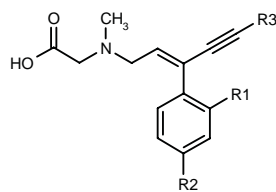
2-[N-[5-(4-Fluorophenyl)-3-phenyl-2-penten-4-ynyl]-N-methylamino]acetic acid

N-[5-(4-Fluorophenyl)-3-phenyl-2-penten-4-ynyl]-N-methylglycine



C20 H18 F N O2; Mol wt: 323.3652

ACTION – Glycine uptake inhibitor, particularly GlyT1 inhibitor, potentially useful for the treatment of schizophrenia, cognitive dysfunction and Alzheimer’s disease. Other specifically claimed diaryl-enynes include the following:



Compound	R1	R2	R3	Formula
324857	H	H	4-NO2-Ph	C ₂₀ H ₁₈ N ₂ O ₄
324858	H	H	3,5-(CF3)2-Ph	C ₂₂ H ₁₇ F ₆ NO ₂
324859	H	H	4-Et-Ph	C ₂₂ H ₂₃ NO ₂
324860	H	H	1-Naph	C ₂₄ H ₂₁ NO ₂
324861	H	H	3,4-(MeO)2-Ph	C ₂₂ H ₂₃ NO ₄
324862	H	CF3	4-i-Pr-Ph	C ₂₄ H ₂₄ F ₃ NO ₂
324863	H	Cl	4-t-Bu-Ph	C ₂₄ H ₂₆ ClNO ₂
324864	Cl	H	4-Et-Ph	C ₂₂ H ₂₂ ClNO ₂

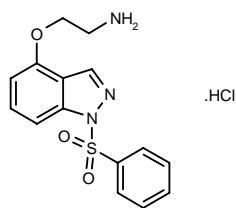
SOURCE – NPS Allelix.

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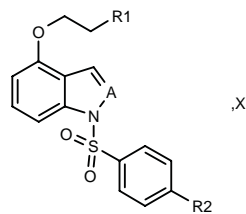
324893

2-[1-(Phenylsulfonyl)-1*H*-indazol-4-yloxy]ethylamine hydrochloride



C15 H15 N3 O3 S . HCl ; Mol wt: 353.8284

ACTION – Agent with affinity for 5-HT₆ receptors that inhibited the binding of [³H]-LSD to human 5-HT₆ receptors expressed in HeLa cells with a K_i of 1.0 nM. Potentially useful for the treatment of CNS disorders such as schizophrenia, depression, attention deficit disorder, Alzheimer’s disease and Parkinson’s disease. Other exemplified benzazole derivatives are:



Compound	R1	R2	A	X	Formula
324894	NH2	H	CH	HCl	C ₁₆ H ₁₆ N ₂ O ₃ .HCl
324895	4-THP-NH	H	CH	HCl	C ₂₁ H ₂₄ N ₂ O ₄ .HCl
324896	(3-MeO-PhCH2)2N	H	CH	HCl	C ₃₂ H ₃₂ N ₂ O ₅ .HCl
324897	3-MeO-PhCH2NH	H	CH	HCl	C ₂₄ H ₂₄ N ₂ O ₄ .HCl
324898	N(Me)2	H	CH	HCl	C ₁₆ H ₂₀ N ₂ O ₃ .HCl
324899	4-morpholinyl	H	CH	HCl	C ₂₀ H ₂₂ N ₂ O ₄ .HCl
324900	1-Pip	H	CH	HCl	C ₂₁ H ₂₄ N ₂ O ₃ .HCl
324901	1-Pip	H	N	HCl	C ₂₀ H ₂₃ N ₃ O ₃ .HCl
324903	1-Pip	NO2	N	HCl	C ₂₀ H ₂₂ N ₄ O ₅ .HCl
324904	1-Pip	F	N	HCl	C ₂₀ H ₂₂ FN ₃ O ₃ .HCl
324905	4-THP-NH	H	N	HCl	C ₂₀ H ₂₃ ClN ₃ O ₄ .HCl
324906	tetrahydro-4-thiopyranyl-NH	H	N	HCl	C ₂₀ H ₂₃ N ₃ O ₃ S ₂ .HCl
324907	1-Pip	NH2	N		C ₂₀ H ₂₄ N ₄ O ₃ S

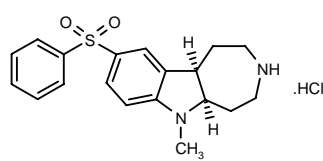
SOURCE – Wyeth.

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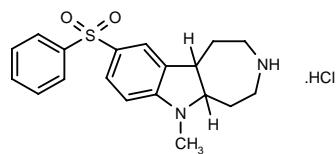
325360

(5a*R*,10b*R*)-6-Methyl-9-(phenylsulfonyl)-1,2,3,4,5,5a,6,10b-octahydroazepino[4,5-*b*]indole hydrochloride



C19 H22 N2 O2 S . HCl; Mol wt: 378.9217

ACTION – Modulator of 5-HT₆ receptors considered to have potential in the treatment of schizophrenia, anxiety, obesity, depression and stress-related diseases, among other disorders associated with 5-HT₆ receptors. Other specifically claimed substituted indolines are:



Compound	Isomer	Formula
325361	5aS,10bS	C ₁₉ H ₂₂ N ₂ O ₂ S.HCl
325363	5aS,10bR	C ₁₉ H ₂₂ N ₂ O ₂ S.HCl
325365	5aR,10bS	C ₁₉ H ₂₂ N ₂ O ₂ S.HCl

SOURCE – Pharmacia.

REFERENCES

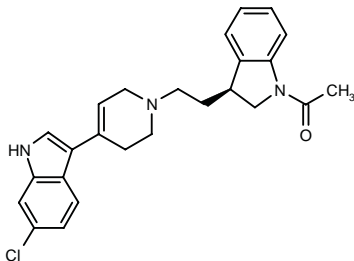
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LU-35-138

286076

3-[1-[2-[(3S)-1-Acetyl-2,3-dihydro-1H-indol-3-yl]ethyl]-1,2,3,6-tetrahydro-4-pyridinyl]-6-chloro-1H-indole

1-Acetyl-3(S)-[2-[4-(6-chloro-1H-indol-3-yl)-1,2,3,6-tetrahydropyridin-1-yl]ethyl]indoline



C25 H26 Cl N3 O; Mol wt: 419.9534

ACTION – Dual-acting dopamine D4 receptor antagonist and 5-HT reuptake inhibitor with high affinity for human D4.2 receptors ($K_i = 4.4$ nM), as compared to rat D2 receptors ($K_i = 75$ nM), and inhibitory activity against [³H]-5-HT uptake in rat brain synaptosomes ($IC_{50} = 8.7$ nM). *In vivo*, it selectively counteracted *d*-amphetamine-induced hyperlocomotion in rats ($ED_{50} = 4.0$ mg/kg/s.c.) without inducing catalepsy or hypomotility ($ED_{50} > 18$ mg/kg s.c.). Currently undergoing phase I clinical studies for the treatment of schizophrenia.

SOURCE – Lundbeck.

REFERENCES

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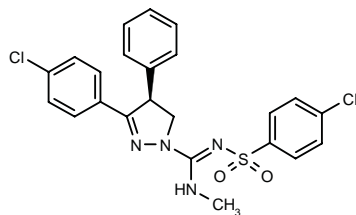
9. *Lundbeck's psychopharmacological drug pipeline*. DailyDrugNews.com (Daily Essentials) 2001, Sept 20.

SLV-319

311665

4-Chloro-N-[1-[3-(4-chlorophenyl)-4(S)-phenyl-4,5-dihydro-1H-pyrazol-1-yl]-1-(methylamino)methylidene]benzenesulfonamide

3-(4-Chlorophenyl)-N²-(4-chlorophenylsulfonyl)-N¹-methyl-4(S)-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamide



C23 H20 Cl2 N4 O2 S; Mol wt: 487.4090

ACTION – Cannabinoid CB₁ receptor antagonist ($pK_i = 8.4$, $pA_2 = 8.4$ for human receptors) with 2,000-fold selectivity over CB₂ receptors ($pK_i < 5$) and good oral activity in a CB agonist-induced hypothermia model ($ID_{50} = 5.5$ mg/kg p.o.), where it showed comparable activity to rimonabant. In addition, compound shows good water solubility, excellent oral bioavailability (60% in rats), good brain penetration and a long duration of action ($t_{1/2} = 8$ h). Currently in phase I development for the treatment of psychosis.

SOURCE – Solvay.

REFERENCES

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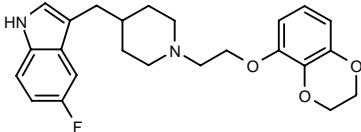
2. Lange, J.H.M. et al. *New approaches for psychosis and obesity treatment: Design, synthesis and SAR of 3,4-diarylpyrazolines as potent, selective and orally active cannabinoid CB1 receptor antagonists*. Drugs Fut 2002, 27(Suppl. A): Abst C62.

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TREATMENT OF MOOD
DISORDERS

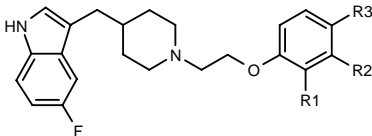
323098

3-[1-[2-(2,3-Dihydro-1,4-benzodioxin-5-yloxy)ethyl]piperidin-4-ylmethyl]-5-fluoro-1*H*-indole

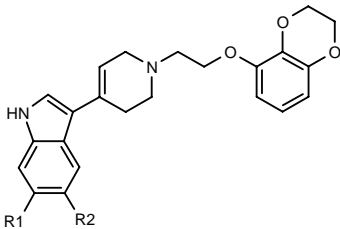


C24 H27 F N2 O3; Mol wt: 410.4863

ACTION – Dual inhibitor of 5-HT_{1A} receptors and 5-HT reuptake, particularly useful for the treatment of depression and anxiety. *In vitro*, compound inhibited the 5-HT transporter and 5-HT_{1A} receptors with K_i values of 0.011 and 168 nM, respectively. Other exemplified aryloxy piperidiny derivatives are:



Compound	R1	R2	R3	Formula
323099	OMe	H	H	C ₂₃ H ₂₇ FN ₂ O ₂
323100	H	-(CH ₂) ₃ -		C ₂₅ H ₂₉ FN ₂ O



Compound	R1	R2	Formula
323101	H	H	C ₂₃ H ₂₄ N ₂ O ₃
323102	H	F	C ₂₃ H ₂₃ FN ₂ O ₃
323103	F	H	C ₂₃ H ₂₃ FN ₂ O ₃

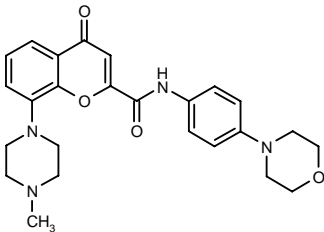
SOURCE – Wyeth.

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1. Mewshaw, R.E. et al. (Wyeth) *Aryloxy piperidiny derivs. for the treatment of depression*. WO 0248105.

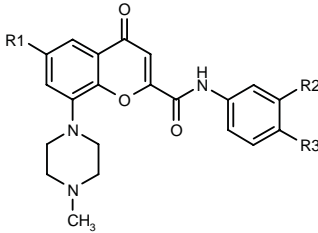
324471

8-(4-Methylpiperazin-1-yl)-*N*-[4-(4-morpholinyl)phenyl]-4-oxo-4*H*-1-benzopyran-2-carboxamide

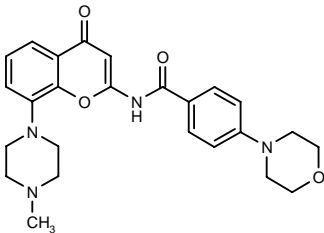


C25 H28 N4 O4; Mol wt: 448.5202

ACTION – 5-HT_{1B} and 5-HT_{1D} receptor antagonist, potentially useful for the treatment of depression, anxiety, eating disorders, dementia, panic disorder, sleep disorders, gastrointestinal, motor or endocrine disorders, vasospasm and sexual dysfunction. Other exemplified 4*H*-1-benzopyran-4-one derivatives are:



Compound	R1	R2	R3	Formula
324472	H	H	4-Ac-1-Piz	C ₂₇ H ₃₁ N ₅ O ₄
324473	H	H	4-F-PhO	C ₂₇ H ₂₄ FN ₃ O ₄
324474	H	H	1-Piz	C ₂₅ H ₂₉ N ₅ O ₃
324475	OMe	H	4-morpholinyl-CO	C ₂₇ H ₃₀ N ₄ O ₆
324476	OMe	H	4-(cyclopentyl-CO)-1-Piz	C ₃₂ H ₃₉ N ₅ O ₅
324477	F	CN	4-morpholinyl	C ₂₆ H ₂₆ FN ₅ O ₄
324478	F	H	1-Piz	C ₂₅ H ₂₈ FN ₅ O ₃



324479: C25 H28 N4 O4

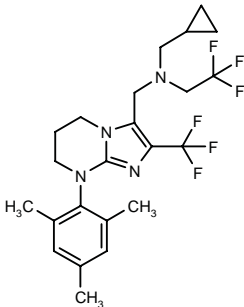
SOURCE – AstraZeneca.

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2. Chapdelaine, M. et al. (AstraZeneca AB) *Therapeutic heterocyclic cpds*. WO 0255012.

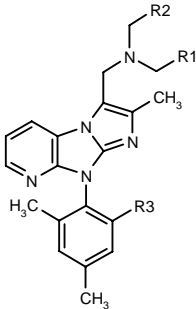
324909

N-(Cyclopropylmethyl)-*N*-(2,2,2-trifluoroethyl)-*N*-[2-(trifluoromethyl)-8-(2,4,6-trimethylphenyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrimidin-3-ylmethyl]amine

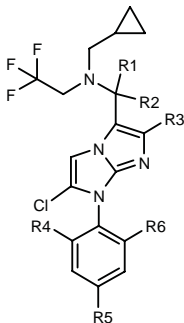


C23 H28 F6 N4; Mol wt: 474.4902

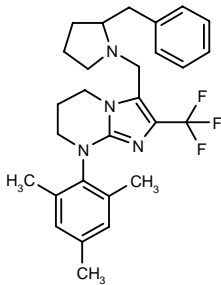
ACTION – Corticotropin-releasing factor CRF₁ receptor antagonist ($K_i < 10$ nM at CRF₁ receptors expressed in IMR-32 cells), potentially useful for the treatment of depression, anxiety, affective disorders, stress disorders, headache, drug abuse, eating disorders, irritable bowel syndrome, hypertension, syndrome X, inflammatory disorders, sleep disorders, epilepsy, stroke, congestive heart failure, osteoporosis, etc. Other exemplified imidazole derivatives are:



Compound	R1	R2	R3	Formula
324910	CH2Ph	Me	Me	C ₂₉ H ₃₃ N ₅
324911	cyclobutyl	Et	Me	C ₂₇ H ₃₅ N ₅
324912	CH2Ph	Et	Cl	C ₂₉ H ₃₂ ClN ₅



Compound	R1	R2	R3	R4	R5=R6	Formula
324914	-O-		Et	H	Cl	C ₂₀ H ₁₈ Cl ₃ F ₃ N ₄ O
324917	H	H	CF3	Me	Me	C ₂₂ H ₂₃ ClF ₆ N ₄



324921: C28 H33 F3 N4

SOURCE – Bristol-Myers Squibb.

REFERENCES

1. Dubowchik, G.M. et al. (Bristol-Myers Squibb Co.) *Imidazolyl derivs. as corticotropin releasing factor inhibitors*. WO 0258704.

NEUROLOGIC DRUGS

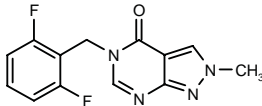
ANTIEPILEPTIC DRUGS

ELB-176

323887

5-(2,6-Difluorobenzyl)-2-methyl-4,5-dihydro-2*H*-pyrazolo[3,4-*d*]pyrimidin-4-one

AWD-34-176



C13 H10 F2 N4 O; Mol wt: 276.2450

ACTION – Anticonvulsant that affects electrical transmission in the brain in part by blocking neuronal sodium channels. It exhibited potent anticonvulsant activity against maximal electroshock-induced seizures in rats ($ED_{50} = 2.1$ mg/kg p.o.), as well as audiogenic-induced clonic seizures in DBA/2 mice and Frings mice ($ED_{50} = 0.68$ and 2.2 mg/kg i.p., respectively). However, compound did not protect against seizures induced by pentylenetetrazol in mice and rats. No tolerance was seen after 5-day oral administration and no motor impairment was seen in the rotarod test ($TD_{50} > 500$ mg/kg p.o.).

SOURCE – elbion.

REFERENCES

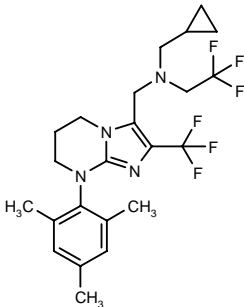
1. Arnold, T. et al. (Arzneimittelwerk Dresden GmbH) *2,5-Dihydro-pyrazolo[3,4-d]-pyrimidin-4-ones with an anticonvulsive action and methods for producing the same*. WO 0218387.

2. Dost, R. and Rundfeldt, C. *AWD 34-176 - A new potential antiepileptic drug*. Epilepsia 2002, 43(Suppl. 8): Abst P219.

3. Unverferth, K. et al. *Synthesis and anticonvulsant activity of AWD 34-176*. Drugs Fut 2002, 27(Suppl. A): Abst P119.

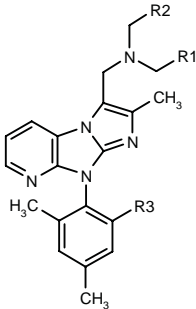
324909

N-(Cyclopropylmethyl)-*N*-(2,2,2-trifluoroethyl)-*N*-[2-(trifluoromethyl)-8-(2,4,6-trimethylphenyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrimidin-3-ylmethyl]amine

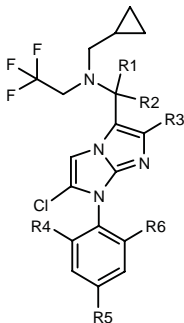


C23 H28 F6 N4; Mol wt: 474.4902

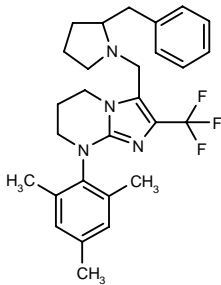
ACTION – Corticotropin-releasing factor CRF₁ receptor antagonist ($K_i < 10$ nM at CRF₁ receptors expressed in IMR-32 cells), potentially useful for the treatment of depression, anxiety, affective disorders, stress disorders, headache, drug abuse, eating disorders, irritable bowel syndrome, hypertension, syndrome X, inflammatory disorders, sleep disorders, epilepsy, stroke, congestive heart failure, osteoporosis, etc. Other exemplified imidazole derivatives are:



Compound	R1	R2	R3	Formula
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324912	CH2Ph	Et	Cl	C ₂₉ H ₃₂ ClN ₅



Compound	R1	R2	R3	R4	R5=R6	Formula
324914	-O-		Et	H	Cl	C ₂₀ H ₁₈ Cl ₃ F ₃ N ₄ O
324917	H	H	CF3	Me	Me	C ₂₂ H ₂₃ ClF ₆ N ₄



324921: C28 H33 F3 N4

SOURCE – Bristol-Myers Squibb.

REFERENCES

1. Dubowchik, G.M. et al. (Bristol-Myers Squibb Co.) *Imidazolyl derivs. as corticotropin releasing factor inhibitors*. WO 0258704.

NEUROLOGIC DRUGS

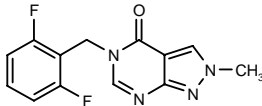
ANTIEPILEPTIC DRUGS

ELB-176

323887

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AWD-34-176



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ACTION – Anticonvulsant that affects electrical transmission in the brain in part by blocking neuronal sodium channels. It exhibited potent anticonvulsant activity against maximal electroshock-induced seizures in rats ($ED_{50} = 2.1$ mg/kg p.o.), as well as audiogenic-induced clonic seizures in DBA/2 mice and Frings mice ($ED_{50} = 0.68$ and 2.2 mg/kg i.p., respectively). However, compound did not protect against seizures induced by pentylenetetrazol in mice and rats. No tolerance was seen after 5-day oral administration and no motor impairment was seen in the rotarod test ($TD_{50} > 500$ mg/kg p.o.).

SOURCE – elbion.

REFERENCES

1. Arnold, T. et al. (Arzneimittelwerk Dresden GmbH) *2,5-Dihydro-pyrazolo[3,4-d]-pyrimidin-4-ones with an anticonvulsive action and methods for producing the same*. WO 0218387.

2. Dost, R. and Rundfeldt, C. *AWD 34-176 - A new potential antiepileptic drug*. Epilepsia 2002, 43(Suppl. 8): Abst P219.

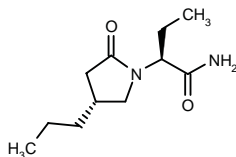
3. Unverferth, K. et al. *Synthesis and anticonvulsant activity of AWD 34-176*. Drugs Fut 2002, 27(Suppl. A): Abst P119.

UCB-34714

321316

2(*S*)-[2-Oxo-4(*R*)-propylpyrrolidin-1-yl]butyramide

(α *S*,4*R*)- α -Ethyl-2-oxo-4-propyl-1-pyrrolidineacetamide



C11 H20 N2 O2; Mol wt: 212.2910

ACTION – Antiepileptic agent, an analogue of levetiracetam with good affinity for the levetiracetam binding site (LBS; $pK_i = 7.1$) and *in vivo* protective activity against audiogenic, maximal electroshock, pentylenetetrazol-induced and corneal kindling seizures ($ED_{50} = 14, 496, 643$ and $5.6 \mu\text{mol/kg}$ i.p., respectively). Compound has entered clinical testing.

SOURCE – UCB.

REFERENCES

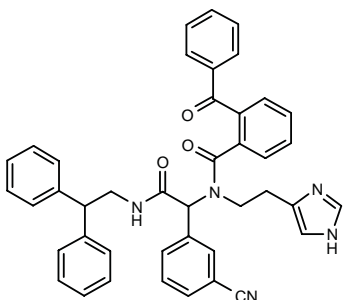
1. Differding, E. et al. (UCB SA) *2-Oxo-1-pyrrolidine derivs., processes for preparing them and their uses*. WO 0162726.
2. Archen, L. et al. *Synthesis of newer Keppra(TM) analogs*. Drugs Fut 2002, 27(Suppl. A): Abst P379.
3. *UCB presents R&D overview*. DailyDrugNews.com (Daily Essentials) 2002, June 21.

TREATMENT OF IMMUNOLOGIC NEUROMUSCULAR DISORDERS

GENZ-29155*

313250

2-Benzoyl-*N*-[1-(3-cyanophenyl)-1-[*N*-(2,2-diphenylethyl)carbamoylmethyl]-*N*-[2-(1*H*-imidazol-4-yl)ethyl]-benzamide



C42 H35 N5 O3; Mol wt: 657.7705

ACTION – Inhibitor of TNF- α -induced apoptosis ($IC_{50} = 0.81 \text{ nM}$ in murine L-929 cells) proven active in two *in vivo* models of TNF- α -mediated pathology: the myelin antigen-induced experimental allergic encephalomyelitis model of multiple sclerosis in mice and lipopolysaccharide/D-galactosamine-induced sepsis in mice; in both experiments, it increased survival in a dose-dependent manner (100% at 75 mg/kg i.p. in the allergic encephalomyelitis model in mice). Potentially useful for the treatment of immune disorders such as multiple sclerosis.

SOURCE – Genzyme.

REFERENCES

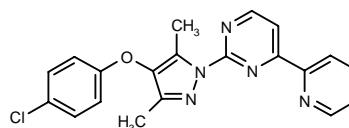
1. Sneddon, S.F. et al. (Genzyme Corp.) *Modulators of TNF- α signaling*. WO 0187849.
2. Hirth, B.H. et al. *Discovery of TNF- α induced apoptosis inhibitors with activity in a murine model of multiple sclerosis: Glycine diamides*. 224th ACS Natl Meet (Aug 18-22, Boston) 2002, Abst MEDI 272.

*Identified compound **313250** Drug Data Rep 2002, 024(02): 0116.

GENZ-34940

324090

2-[4-(4-Chlorophenoxy)-3,5-dimethyl-1*H*-pyrazol-1-yl]-4-(2-pyridyl)pyrimidine



C20 H16 Cl N5 O; Mol wt: 377.8334

ACTION – An inhibitor of TNF- α -induced apoptosis ($IC_{50} = 38 \text{ nM}$ in a cell-based assay) able to significantly delay the induction of experimental acute allergic encephalomyelitis (EAE) in a myelin antigen (PLP)-induced EAE model of multiple sclerosis in mice; a modest improvement in survival rate in comparison with the control group (63% vs. 44%) was found. Potentially useful for the treatment of chronic immune or inflammatory diseases including multiple sclerosis, inflammatory bowel disease and rheumatoid arthritis.

SOURCE – Genzyme.

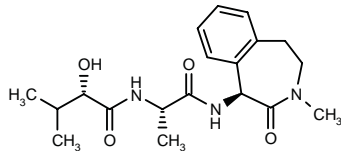
REFERENCES

1. Sneddon, S.F. et al. (Genzyme Corp.) *Modulators of TNF- α signaling*. WO 0187849.
2. Kane, J.L. Jr. et al. *Discovery of TNF- α induced apoptosis inhibitors with activity in a murine model of multiple sclerosis: Pyrazole series*. 224th ACS Natl Meet (Aug 18-22, Boston) 2002, Abst MEDI 273.

TREATMENT OF COGNITION
DISORDERS

322926

*N*²-[2(*S*)-Hydroxy-3-methylbutyryl]-*N*¹-[3-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-3-benzazepin-1(*S*)-yl]-L-alaninamide



C19 H27 N3 O4; Mol wt: 361.4393

ACTION – Inhibitor of the synthesis and/or release of β -amyloid peptide (A β) with potential in the prevention and treatment of Alzheimer’s disease.

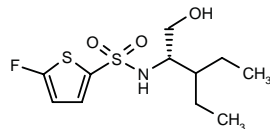
SOURCES – Elan; Lilly.

REFERENCES

1. Audia, J.E. et al. (Eli Lilly and Company; Elan Pharmaceuticals, Inc.) *Lactam cpd.* WO 0247671.
2. Koenig, T.M. et al. (Eli Lilly and Company) *Lactam cpd.* WO 0240508.

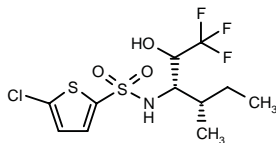
324579

N-[2-Ethyl-1(*S*)-(hydroxymethyl)butyl]-5-fluorothiophene-2-sulfonamide



C11 H18 F N O3 S2; Mol wt: 295.3972

ACTION – Agent with the ability to inhibit the production of β -amyloid peptide (A β) from amyloid precursor protein (APP), shown to induce an increase in APP in CHO-K1 cells in a luciferase reporter gene assay. Potentially useful for the treatment of Alzheimer’s disease, amyloid angiopathy, cerebral amyloid angiopathy, systemic amyloidosis, hereditary cerebral hemorrhage with amyloidosis of the Dutch type, inclusion body myositis and Down’s syndrome. Another exemplified heterocyclic sulfonamide derivative is:



324581: C11 H15 Cl F3 N O3 S2

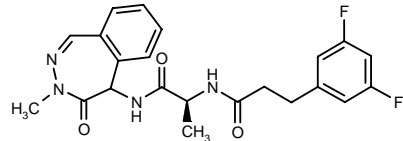
SOURCES – ArQule; Wyeth.

REFERENCES

1. Kreft, A.F. et al. (Wyeth;ArQule, Inc.) *Heterocyclic sulfonamide inhibitors of β amyloid production.* WO 0257252.

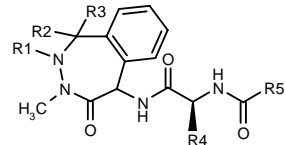
325068

*N*²-[3-(3,5-Difluorophenyl)propionyl]-*N*¹-(3-methyl-4-oxo-4,5-dihydro-3*H*-2,3-benzodiazepin-5-yl)-L-alaninamide



C22 H22 F2 N4 O3; Mol wt: 428.4368

ACTION – Agent with the ability to inhibit the production of β -amyloid peptide (A β ; IC₅₀ = 10 nM). Potentially useful for the treatment of Alzheimer’s disease. Other exemplified benzodiazepinone derivatives are:



Compound	R1	R2	R3	R4	R5	Formula
325069	i-Pr	-O-	i-Bu		3-thienyl-CH2CH2	C ₂₆ H ₃₄ N ₄ O ₄ S
325070	i-Pr	-O-	i-Pr		3-thienyl-CH2CH2	C ₂₅ H ₃₂ N ₄ O ₄ S
325071	bond		H	Me	(S)-3,5-(F)2-PhCH2CH(OH)	C ₂₂ H ₂₂ F ₂ N ₄ O ₄
325072	bond		H	Me	(R)-3,5-(F)2-PhCH2CH(OH)	C ₂₂ H ₂₂ F ₂ N ₄ O ₄
325073	bond		H	Me	3-thienyl-CH2CH2	C ₂₀ H ₂₂ N ₄ O ₃ S
325074	bond		H	Me	2-thienyl-CH2	C ₁₉ H ₂₀ N ₄ O ₃ S
325075	bond		H	Me	3-Cl-PhCH2CH2	C ₂₁ H ₂₁ ClN ₄ O ₃
325076	i-Pr		-O-	Me	3-F-PhCH2CH2	C ₂₅ H ₂₈ FN ₄ O ₄
325077	bond		H	i-Bu	3-thienyl-CH2	C ₂₂ H ₂₆ N ₄ O ₃ S
325078	bond		H	i-Bu	3,5-(F)2-PhCH2CH2	C ₂₄ H ₂₆ F ₂ N ₄ O ₃
325079	bond		H	i-Bu	(S)-CH(OH)Ph	C ₂₄ H ₂₈ N ₄ O ₄
325080	bond		H	i-Bu	2-thienyl-CH2	C ₂₂ H ₂₆ N ₄ O ₃ S
325081	bond		H	i-Bu	3-F-PhCH2CH2	C ₂₅ H ₂₈ FN ₄ O ₃
325082	bond		H	i-Bu	3-Cl-PhCH2CH2	C ₂₅ H ₂₉ ClN ₄ O ₃

SOURCE – Bristol-Myers Squibb.

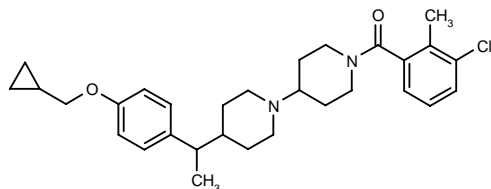
REFERENCES

1. Chaturvedula, P.V. et al. (Bristol-Myers Squibb Co.) *Benzodiazepinone β -amyloid inhibitors: Arylacetamidoalanyl derivs.* US 6432944.

SCH-226206

323632

1-(3-Chloro-2-methylphenyl)-1-[4-[1-[4-(cyclopropylmethoxy)phenyl]ethyl]-1,4'-bipiperidin-1'-yl]methanone



C30 H39 Cl N2 O2; Mol wt: 495.1031

ACTION – Potent muscarinic M₂ receptor antagonist (K_i = 0.52 nM) with 125- and 98-fold selectivity over M₁ and M₃ receptors, respectively, and an oral bioavailability of 54% in rats and 43% in dogs. Potentially useful for the treatment of Alzheimer's disease.

SOURCE – Schering-Plough.

REFERENCES

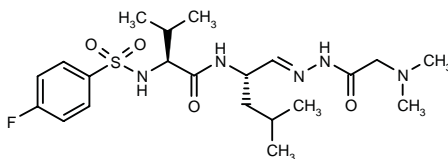
1. Hey, J.A. and Aslanian, R.G. (Schering Corp.) *Use of dual H₂/M₂ antagonists in the treatment of cognition deficit disorders*. WO 0272093.

2. Wang, Y. et al. *Sch 226206: A potent, selective and orally efficacious M2 muscarinic receptor antagonist for the treatment of Alzheimer's disease*. 224th ACS Natl Meet (Aug 18-22, Boston) 2002, Abst MED1 6.

SNJ-1558

322850

N¹-[1(S)-[2-(Dimethylamino)acetylhydrazonomethyl]-3-methylbutyl]-N²-(4-fluorophenylsulfonyl)-L-valinamide



C21 H34 F N5 O4 S; Mol wt: 471.5946

ACTION – μ -Calpain inhibitor (IC₅₀ = 0.37 μ M) with good water solubility in buffer at pH 4 and 5 (4.33 and 1.98 mg/ml, respectively). Potentially useful for the treatment of Alzheimer's disease, muscular dystrophy and cataracts.

SOURCE – Senju.

REFERENCES

1. Nakamura, M. and Inoue, J. (Senju Pharmaceuticals Co., Ltd.) *Hydrazone derivs. and use thereof in medicines*. WO 0248096.

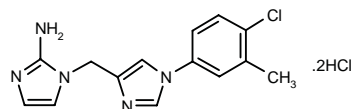
2. Nakamura, M. and Inoue, J. *Exploration of peptidyl hydrazones as water-soluble calpain inhibitors*. Bioorg Med Chem Lett 2002, 12(12): 1603.

3. Nakamura, M. and Inoue, J. *Exploration of peptidyl hydrazones as water-soluble calpain inhibitors*. Drugs Fut 2002, 27(Suppl. A): Abst P390.

TREATMENT OF CEREBROVASCULAR DISEASES

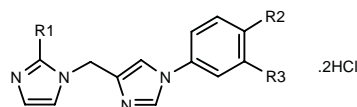
325318

1-[1-(4-Chloro-3-methylphenyl)-1H-imidazol-4-ylmethyl]-1H-imidazol-2-amine dihydrochloride



C14 H14 Cl N5 . 2HCl; Mol wt: 360.6744

ACTION – Selective antagonist of NMDA NR2B receptors found to inhibit [³H]-Ro-25-6981 binding to NMDA receptors in rat brain preparations with an IC₅₀ of 0.001 μ M. Potentially useful for the treatment of acute and chronic neurodegenerative disorders such as stroke, brain trauma, Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, neurodegeneration associated with bacterial or viral infection, depression and pain. Other exemplified imidazole derivatives are:



Compound	R1	R2	R3	Formula
325320	Pr	Cl	Cl	C ₁₆ H ₁₆ Cl ₂ N ₄ .2HCl
325321	Et	Cl	Me	C ₁₆ H ₁₇ ClN ₄ .2HCl
325322	Me	Cl	Me	C ₁₅ H ₁₅ ClN ₄ .2HCl
325323	H	Cl	Me	C ₁₄ H ₁₃ ClN ₄ .2HCl
325324	Me	-(CH ₂) ₃ -		C ₁₇ H ₁₈ N ₄ .2HCl
325326	Et	H	SCF ₃	C ₁₆ H ₁₅ F ₃ N ₄ S.2HCl
325327	Et	H	CF ₂ Me	C ₁₇ H ₁₈ F ₂ N ₄ .2HCl
325328	Me	H	CF ₂ Me	C ₁₆ H ₁₆ F ₂ N ₄ .2HCl
325330	Me	F	CF ₂ Me	C ₁₆ H ₁₅ F ₃ N ₄ .2HCl

SOURCE – Roche.

REFERENCES

1. Alanine, A. et al. (F. Hoffmann-La Roche AG) *Imidazole derivs*. WO 0260877.

E-SELECTIN VACCINE

324649

Vaccine consisting of human E-selectin protein

ACTION – Human E-selectin-based vaccine that targets inflammation in blood vessels and was able to prevent stroke in spontaneously hypertensive stroke-prone rats after nasal instillation. The vaccine induced mucosal tolerance to E-selectin, suppressing local blood vessel activation and inflammation. Repeated transmucosal administration of the vaccine strongly reduced the number and magnitude of ischemic strokes and completely prevented hemorrhagic stroke. Repeated treatment with the vaccine was required for long-term stroke prevention. No effect on blood pressure was seen in the booster group.

SOURCES – National Institutes of Health, Bethesda, MD (US); Novavax.

REFERENCES

1. Hallenbeck, J.M. et al. (US Department of Health & Human Services) *Methods for preventing strokes by inducing tolerance to E-selectin*. WO 0189557.

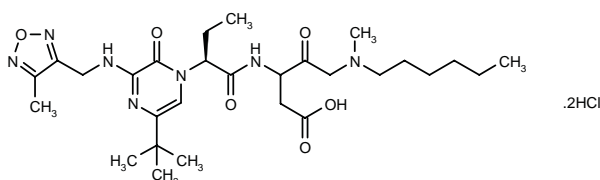
2. Takeda, H. et al. *Induction of mucosal tolerance to E-selectin prevents ischemic and hemorrhagic stroke in spontaneously hypertensive genetically stroke-prone rats*. Stroke 2002, 33(9): 2156.

MF-826

311243

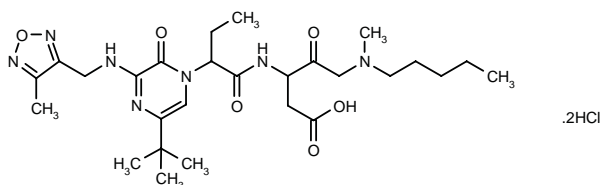
3-[2(S)-[5-*tert*-Butyl-3-(4-methyl-1,2,5-oxadiazol-3-yl)methylamino]-2-oxo-1,2-dihydropyrazin-1-yl]butyramido]-5-(*N*-hexyl-*N*-methylamino)-4-oxopentanoic acid dihydrochloride

M-826



C28 H45 N7 O6 . 2HCl; Mol wt: 648.6283

ACTION – Neuroprotective agent proven to potently, selectively and reversibly inhibit caspase 3 ($IC_{50} = 52$ nM) and apoptosis in cell-based assays ($IC_{50} = 0.03$ - 0.12 μ M for inhibition of DNA fragmentation induced by camptothecin or etoposide in human teratocarcinoma cells). In rats with neonatal hypoxic-ischemic brain injury, intracerebroventricular injection of compound inhibited cortical and hippocampal caspase 3 activation and other apoptotic features including DNA fragmentation and brain tissue loss; it did not prevent calpain activation in the cortex. Another related compound is:



323898^{1,4}: C27 H43 N7 O6 . 2HCl

SOURCE – Merck Frosst.

REFERENCES

1. Han, Y. et al. (Merck Frosst Canada Inc.) *Pyrazinones, compsns. containing such cpds*. EP 1202976, WO 0105772.

2. Han, B.H. et al. *MF-826, a selective caspase-3 inhibitor, attenuates apoptosis following neonatal hypoxia-ischemia*. Soc Neurosci Abst 2001, 27 Abst 763.2.

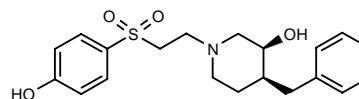
3. Han, B.H. et al. *Selective, reversible caspase-3 inhibitor is neuroprotective and reveals distinct pathways of cell death after neonatal hypoxic-ischemic brain injury*. J Biol Chem 2002, 277(33): 30128.

4. Han, Y. *Discovery of novel pyrazinone derivatives as potent and selective caspase-3 inhibitors*. 224th ACS Natl Meet (Aug 18-22, Boston) 2002, Abst MEDI 428.

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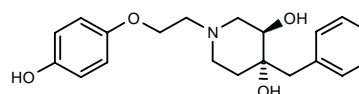
324374

4(S)-Benzyl-1-[2-(4-hydroxyphenylsulfonyl)ethyl]piperidin-3(S)-ol



C20 H25 N O4 S; Mol wt: 375.4865

ACTION – Neuroprotective agent, a potent NMDA NR1/2B receptor antagonist ($IC_{50} = 14$ nM) with good selectivity over potassium HERG channels ($IC_{50} = 24$ μ M) and *in vivo* activity in animal models of stroke at doses not inducing prolongation of the Q-T interval. Another related compound is:



324367^{1,2,4}: C20 H25 N O4

SOURCE – Roche.

REFERENCES

1. Alanine, A. et al. (F. Hoffmann-La Roche AG) *Ethanesulfonyl-piperidine derivs*. EP 1189886, WO 0075109.

2. Alanine, A. et al. (Hoffmann-La Roche, Inc.) *Neuroprotective subst. piperidine cpds. with activity as NMDA NR2B subtype selective antagonists*. US 6432985.

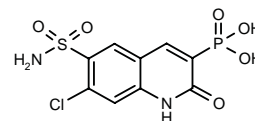
3. Cramer, Y. et al. (F. Hoffmann-La Roche AG) *Piperidine and piperazine cpds. for use in the treatment of Alzheimer*. EP 1136475.

4. Jaeschke, G. et al. *Synthesis and biological evaluation of β -aminosulfones as novel NMDA-NR1/2B subtype selective antagonists*. Drugs Fut 2002, 27(Suppl. A): Abst C76.

S-34730-1*

308513

(7-Chloro-2-oxo-6-sulfamoyl-1,2-dihydroquinolin-3-yl)-phosphonic acid



C9 H8 Cl N2 O6 P S; Mol wt: 338.6632

ACTION – Potent and selective AMPA receptor antagonist with IC_{50} values of 0.2 and > 300 μ M, respectively, at AMPA and glycine-site NMDA receptors. It displayed strong anticonvulsant activity against audiogenic seizures in DBA/2 mice ($ED_{50} = 3.3$ mg/kg i.p.). Currently under evaluation as a potential treatment for stroke.

SOURCE – Servier.

REFERENCES

1. Cordi, A. et al. (ADIR et Cie.) *Derivs. of 6-sulfamoyl-3-quinolyl phosphonic acids, process for their preparation and pharmaceutical compsns. containing them*. EP 1125941, FR 2805260, JP 2001253892.

2. Desos, P. et al. *Novel quinolone-phosphonate AMPA antagonists devoid of nephrotoxicity*. Drugs Fut 2002, 27(Suppl. A): Abst P212.

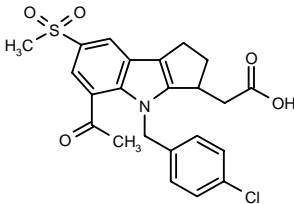
*Identified compound **308513** Drug Data Rep 2001, 023(10): 0964.

RESPIRATORY DRUGS

TREATMENT OF UPPER
RESPIRATORY TRACT DISORDERS

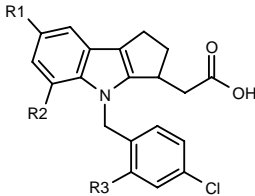
323239

(±)-2-[5-Acetyl-4-(4-chlorobenzyl)-7-(methylsulfonyl)-1,2,3,4-tetrahydrocyclopenta[*b*]indol-3-yl]acetic acid



C23 H22 Cl N O5 S; Mol wt: 459.9478

ACTION – Prostaglandin D₂ (DP) receptor antagonist with the ability to prevent the nasal and pulmonary congestion effects of D-type prostaglandins. Claimed for use in the treatment of nasal congestion, allergic asthma and allergic rhinitis. Other exemplified cyclopenta[*b*]indole compounds are:



Compound	R1	R2	R3	Isomer	Formula
323240	SO2Me	Ac	H	(+)	C ₂₃ H ₂₂ ClNO ₅ S
323241	SO2Me	Ac	H	(-)	C ₂₃ H ₂₂ ClNO ₅ S
323242	SO2Me	CH(OH)Me	H	A	C ₂₃ H ₂₄ ClNO ₅ S
323243	SO2Me	CH(OH)Me	H	B	C ₂₃ H ₂₄ ClNO ₅ S
323244	SO2Me	Br	Cl	racemic	C ₂₁ H ₁₈ BrCl ₂ NO ₄ S
323245	SO2Me	vinyl	H	racemic	C ₂₃ H ₂₂ ClNO ₄ S
323246	SO2Me	cyclopropyl	H	racemic	C ₂₄ H ₂₄ ClNO ₄ S
323247	SO2Me	2-thienyl	H	racemic	C ₂₅ H ₂₂ ClNO ₄ S ₂
323248	SO2N(Me)2	H	H	racemic	C ₂₂ H ₂₃ ClN ₂ O ₄ S
323249	F	Br	H	racemic	C ₂₀ H ₁₆ BrClFNO ₂
323250	F	Br	H	(+)	C ₂₀ H ₁₆ BrClFNO ₂
323251	F	Br	H	(-)	C ₂₀ H ₁₆ BrClFNO ₂

SOURCE – Merck Frosst.

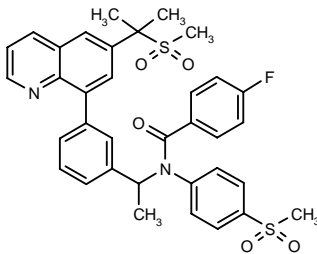
REFERENCES

1. Labelle, M. et al. (Merck Frosst Canada Inc.) *Cyclopentaindoles, compsns. containing such cpds. and methods of treatment*. US 6410583.

ASTHMA THERAPY

324049

4-Fluoro-*N*-[1-[3-[6-[1-methyl-1-(methylsulfonyl)ethyl]-quinolin-8-yl]phenyl]ethyl]-*N*-[4-(methylsulfonyl)phenyl]-benzamide



C35 H33 F N2 O5 S2; Mol wt: 644.7847

ACTION – Phosphodiesterase type 4 (PDE4) inhibitor with nanomolar activity in an enzymatic assay (IC₅₀ = 0.6-2.3 nM) and a cell-based assay (IC₅₀ = 0.56 μM for inhibition of lipopolysaccharide [LPS]-induced TNF-α production in human whole blood). Compound exhibited good pharmacokinetics in rats and monkeys, with respective oral bioavailabilities of 67 and 98%. *In vivo* experiments showed that a dose of 30 μg/kg inhibited ovalbumin-induced bronchoconstriction in sensitized guinea pigs by 74%. Potentially useful for the treatment of asthma.

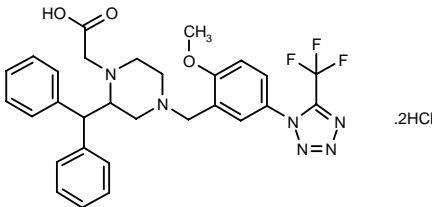
SOURCE – Merck Frosst.

REFERENCES

1. Lacombe, P. et al. *Heteroatom-bridged substituted 8-arylquinolines as potent PDE IV inhibitors*. 224th ACS Natl Meet (Aug 18-22, Boston) 2002, Abst MEDI 328.

324319

2-[2-Diphenylmethyl-4-[2-methoxy-5-[5-(trifluoromethyl)-1*H*-tetrazol-1-yl]benzyl]piperazin-1-yl]acetic acid dihydrochloride



C29 H29 F3 N6 O3 . 2HCl; Mol wt: 639.5029

REFERENCES

1. Cordi, A. et al. (ADIR et Cie.) *Derivs. of 6-sulfamoyl-3-quinolyl phosphonic acids, process for their preparation and pharmaceutical compsns. containing them*. EP 1125941, FR 2805260, JP 2001253892.

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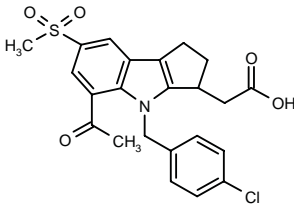
*Identified compound **308513** Drug Data Rep 2001, 023(10): 0964.

RESPIRATORY DRUGS

TREATMENT OF UPPER
RESPIRATORY TRACT DISORDERS

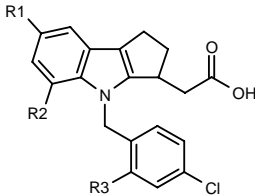
323239

(±)-2-[5-Acetyl-4-(4-chlorobenzyl)-7-(methylsulfonyl)-1,2,3,4-tetrahydrocyclopenta[*b*]indol-3-yl]acetic acid



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ACTION – Prostaglandin D₂ (DP) receptor antagonist with the ability to prevent the nasal and pulmonary congestion effects of D-type prostaglandins. Claimed for use in the treatment of nasal congestion, allergic asthma and allergic rhinitis. Other exemplified cyclopenta[*b*]indole compounds are:



Compound	R1	R2	R3	Isomer	Formula
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323241	SO ₂ Me	Ac	H	(-)	C ₂₃ H ₂₂ ClNO ₅ S
323242	SO ₂ Me	CH(OH)Me	H	A	C ₂₃ H ₂₄ ClNO ₅ S
323243	SO ₂ Me	CH(OH)Me	H	B	C ₂₃ H ₂₄ ClNO ₅ S
323244	SO ₂ Me	Br	Cl	racemic	C ₂₁ H ₁₈ BrCl ₂ NO ₄ S
323245	SO ₂ Me	vinyl	H	racemic	C ₂₃ H ₂₂ ClNO ₄ S
323246	SO ₂ Me	cyclopropyl	H	racemic	C ₂₄ H ₂₄ ClNO ₄ S
323247	SO ₂ Me	2-thienyl	H	racemic	C ₂₅ H ₂₂ ClNO ₄ S ₂
323248	SO ₂ N(Me) ₂	H	H	racemic	C ₂₂ H ₂₃ ClN ₂ O ₄ S
323249	F	Br	H	racemic	C ₂₀ H ₁₆ BrClFNO ₂
323250	F	Br	H	(+)	C ₂₀ H ₁₆ BrClFNO ₂
323251	F	Br	H	(-)	C ₂₀ H ₁₆ BrClFNO ₂

SOURCE – Merck Frosst.

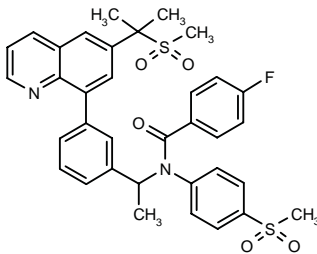
REFERENCES

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ASTHMA THERAPY

324049

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C35 H33 F N2 O5 S2; Mol wt: 644.7847

ACTION – Phosphodiesterase type 4 (PDE4) inhibitor with nanomolar activity in an enzymatic assay (IC₅₀ = 0.6-2.3 nM) and a cell-based assay (IC₅₀ = 0.56 μM for inhibition of lipopolysaccharide [LPS]-induced TNF-α production in human whole blood). Compound exhibited good pharmacokinetics in rats and monkeys, with respective oral bioavailabilities of 67 and 98%. *In vivo* experiments showed that a dose of 30 μg/kg inhibited ovalbumin-induced bronchoconstriction in sensitized guinea pigs by 74%. Potentially useful for the treatment of asthma.

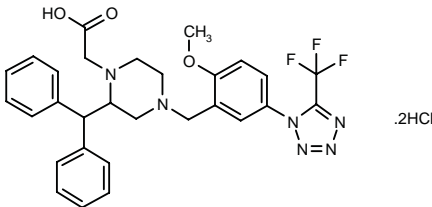
SOURCE – Merck Frosst.

REFERENCES

1. Lacombe, P. et al. *Heteroatom-bridged substituted 8-arylquinolines as potent PDE IV inhibitors*. 224th ACS Natl Meet (Aug 18-22, Boston) 2002, Abst MEDI 328.

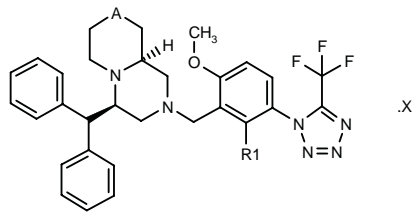
324319

2-[2-Diphenylmethyl-4-[2-methoxy-5-[5-(trifluoromethyl)-1*H*-tetrazol-1-yl]benzyl]piperazin-1-yl]acetic acid dihydrochloride

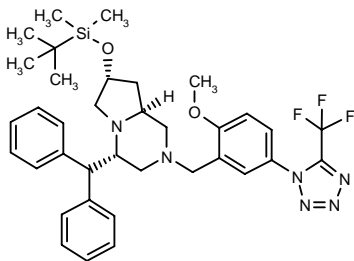


C29 H29 F3 N6 O3 . 2HCl; Mol wt: 639.5029

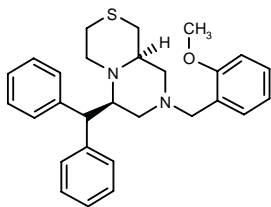
ACTION – Tachykinin antagonist expected to be useful for the treatment of tachykinin-mediated disorders, particularly respiratory diseases such as asthma, bronchitis, rhinitis, etc., as well as ophthalmic and inflammatory diseases. Other exemplified benzhydryl derivatives are:



Compound	R1	A	X	Formula
324326	H	-N(COCH2OH)-	2HCl	C ₃₂ H ₃₄ F ₃ N ₇ O ₃ ·2HCl
324327	H	-N[CON(Me)2]-	2HCl	C ₃₃ H ₃₇ F ₃ N ₈ O ₂ ·2HCl
324328	H	-N(COCH2NHCOCH2OCH2Ph)-		C ₄₁ H ₄₃ F ₃ N ₈ O ₄
324329	H	-N[(S)-COCH(Me)OSi(Ph)2(t-Bu)]-		C ₄₉ H ₅₄ F ₃ N ₇ O ₃ Si
324330	H	-S-	2HCl	C ₃₀ H ₃₁ F ₃ N ₆ OS·2HCl
324332	OMe	-NH-	3HCl	C ₃₁ H ₃₄ F ₃ N ₇ O ₂ ·3HCl



324321: C36 H45 F3 N6 O2 Si



324331: C28 H32 N2 O S

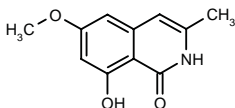
SOURCE – Fujisawa.

REFERENCES

1. Take, K. et al. (Fujisawa Pharmaceutical Co., Ltd.) *1-(2-Methoxybenzyl)-3-benzhydrylpiperazines as tachykinin antagonists*. WO 0255518.

324461

8-Hydroxy-6-methoxy-3-methylisoquinolin-1(2H)-one



C11 H11 N O3; Mol wt: 205.2119

ACTION – Phosphodiesterase type 4 (PDE4) inhibitor proven to inhibit PDE1, PDE2, PDE3, PDE4 and PDE5 isozymes by 38, 19, 9, 41 and 21%, respectively, at 100 μ M. In pig tracheal smooth muscle preparations, compound concentration-dependently inhibited histamine-induced contractions by 21, 85 and 101%, respectively, at

concentrations of 1, 10 and 100 μ M. Potentially useful for the treatment of asthma, bronchitis, angina pectoris, arrhythmia, allergy and rheumatism, among other PDE4-mediated disorders.

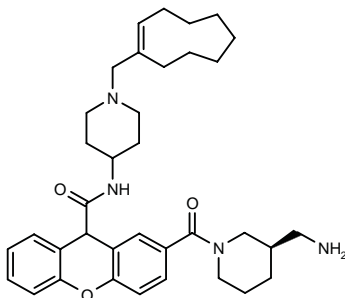
SOURCE – Mercian.

REFERENCES

1. Nakajima, T. et al. (Mercian Corp.) *Phosphodiesterase inhibitors*. JP 2002161036.

324516

2-[3(R)-(Aminomethyl)piperidin-1-ylcarbonyl]-N-[1-(1-cyclononen-1-ylmethyl)piperidin-4-yl]-9H-xanthene-9-carboxamide



C36 H48 N4 O3; Mol wt: 584.8002

ACTION – A representative compound from a series of xanthene carboxamide derivatives that acts as a chemokine CCR1 receptor antagonist, giving IC₅₀ values of 1.8 and 3900 nM, respectively, at CCR1 and CCR3 receptors expressed in CHO cells in radioligand binding assays. In functional assays, it demonstrated CCR1 receptor-antagonist activity with an IC₅₀ value of 13 nM. Potentially useful for the treatment of bronchial asthma, atopic dermatitis, rheumatoid arthritis, multiple sclerosis, AIDS, ischemia–reperfusion injury and cancer, among other CCR1-mediated disorders.

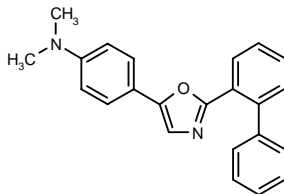
SOURCE – Banyu.

REFERENCES

1. Naya, A. et al. (Banyu Pharmaceutical Co., Ltd.) *Novel xanthene carboxamide derivs*. JP 2002179676.

324739

N-[4-[2-(2-Biphenyl)oxazol-5-yl]phenyl]-N,N-dimethylamine



C23 H20 N2 O; Mol wt: 340.4240

ACTION – A representative compound from a series of diphenyloxazole derivatives with the ability to inhibit the production of IL-4. Potentially useful for the treatment of atopic dermatitis, bronchial asthma, allergic rhinitis, food allergy, anaphylaxis and allergic conjunctivitis, among other IL-4-mediated disorders.

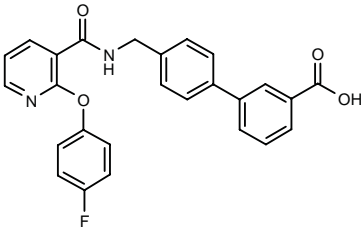
SOURCE – Sankyo.

REFERENCES

1. Shiraishi, A. et al. (Sankyo Co., Ltd.) *Diphenyloxazole derivs.* JP 2002226466.

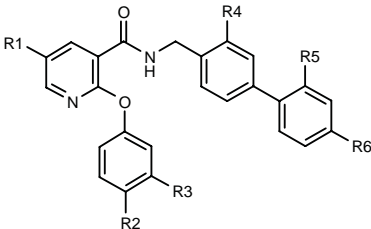
325294

4'-[2-(4-Fluorophenoxy)pyridin-3-ylcarboxamidomethyl]-biphenyl-3-carboxylic acid

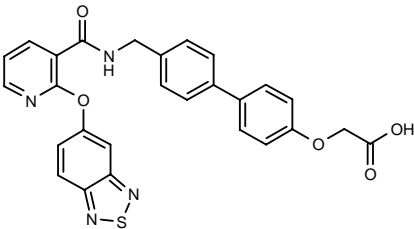


C26 H19 F N2 O4; Mol wt: 442.4441

ACTION – Phosphodiesterase type 4 (PDE4) inhibitor, potentially useful for the treatment of asthma, chronic bronchitis and chronic obstructive pulmonary disease, among other PDE4-related disorders. Other specifically claimed compounds include the following:



Compound	R1	R2	R3	R4	R5	R6	Formula
325298	H	-OCH2O-	H	F		OCH(Me)CO2H	C ₂₉ H ₂₃ FN ₂ O ₇
325299	H	-OCH2O-	F	OCH(Me)-CO2H		H	C ₂₉ H ₂₃ FN ₂ O ₇
325300	H	H	CN	F		CH2CO2H	C ₂₈ H ₂₀ FN ₃ O ₄
325301	F	H	OMe	F	H	5-Me-4H-1,2,4-triazol-3-yl-CONHCH2	C ₃₁ H ₂₆ F ₂ N ₆ O ₄
325303	H	F	Cl	H	F	OCH(Me)-CH2CO2H	C ₂₉ H ₂₃ ClF ₂ N ₂ O ₅
325304	H	-OCH2O-	H	F		2-quinolinyl-CH2NHCO	C ₃₇ H ₂₇ FN ₄ O ₅
325305	H	F	H	H	F	CH(Me)2OH	C ₂₈ H ₂₄ F ₂ N ₂ O ₃



325297: C27 H20 N4 O5 S

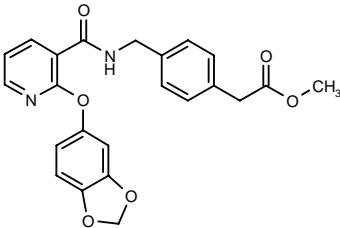
SOURCE – Pfizer.

REFERENCES

1. Chambers, R.J. et al. (Pfizer Products Inc.) *Nicotinamide biaryl derivs. useful as inhibitors of PDE4 isozymes.* WO 0260875.

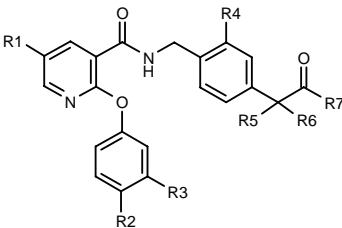
325387

2-[4-[2-(1,3-Benzodioxol-5-yloxy)pyridin-3-ylcarboxamido-methyl]phenyl]acetic acid methyl ester

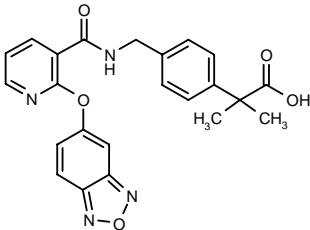


C23 H20 N2 O6; Mol wt: 420.4190

ACTION – Phosphodiesterase type 4 (PDE4) inhibitor, potentially useful for the treatment of asthma, chronic bronchitis and chronic obstructive pulmonary disease, among other PDE4-related disorders. Other specifically claimed nicotinamide derivatives include the following:



Compound	R1	R2	R3	R4	R5	R6	R7	Formula
325389	H	-OCH2O-		F		-(CH2)3-	OEt	C ₂₇ H ₂₅ FN ₂ O ₆
325390	H	-OCH2O-		H	Me	Me	OH	C ₂₄ H ₂₂ N ₂ O ₆
325391	H	F	H	F	Me	Me	OH	C ₂₃ H ₂₀ F ₂ N ₂ O ₄
325392	F	-OCH2O-		OMe	Me	Me	OH	C ₂₅ H ₂₃ FN ₂ O ₇
325393	H	-OCH2O-		F		-CH2CH2-	OH	C ₂₄ H ₁₉ FN ₂ O ₆
325395	H	-OCH2O-		F	Me	Me	NH2	C ₂₄ H ₂₂ FN ₃ O ₅
325396	H	-OCH2O-		H	Me	Me	NHEt	C ₂₆ H ₂₇ N ₃ O ₅



325394: C23 H20 N4 O5

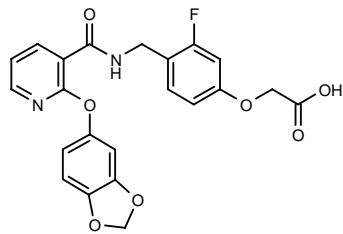
SOURCE – Pfizer.

REFERENCES

1. Chambers, R.J. et al. (Pfizer Products Inc.) *Nicotinamide derivs. and their mimetics as inhibitors of PDE4 isozymes.* EP 1229034.

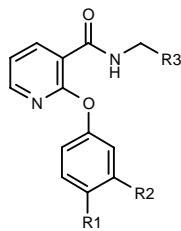
325400

2-[4-[2-(1,3-Benzodioxol-5-yloxy)pyridin-3-ylcarboxamido-methyl]-3-fluorophenoxy]acetic acid

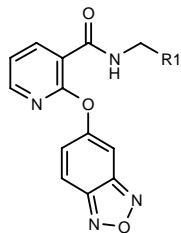


C22 H17 F N2 O7; Mol wt: 440.3813

ACTION – Phosphodiesterase type 4 (PDE4) inhibitor, potentially useful for the treatment of asthma, chronic bronchitis and chronic obstructive pulmonary disease, among other PDE4-related disorders. Other specifically claimed compounds include the following:



Compound	R1	R2	R3	Formula
325403	-OCH2O-		(S)-2-F-4-[CO2HCH(Me)CH2O]-Ph	C ₂₄ H ₂₁ FN ₂ O ₇
325404	F	H	(R)-4-[CO2HCH(Me)O]-1-cyclohexenyl	C ₂₂ H ₂₃ FN ₂ O ₅
325406	H	CN	4-[CO2HC(Me)2O]-cyclohexyl	C ₂₄ H ₂₇ N ₃ O ₅
325408	-OCH2O-		3-[CO2HCH(Me)O]-1-cyclopentenyl	C ₂₂ H ₂₂ N ₂ O ₇
325409	-OCH2O-		2-F-4-[CO2HC(Me)2O]-Ph	C ₂₄ H ₂₁ FN ₂ O ₇
325410	H	OMe	(R)-2-F-4-[CO2HCH(Me)O]-Ph	C ₂₃ H ₂₁ FN ₂ O ₆



Compound	R1	Formula
325401	(R)-2-F-4-[CO2HCH(Me)O]-Ph	C ₂₂ H ₁₇ FN ₄ O ₆
325405	(R)-4-[CO2HCH(Me)O]-cyclohexyl	C ₂₂ H ₂₄ N ₄ O ₆

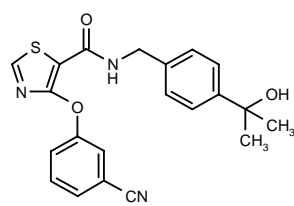
SOURCE – Pfizer.

REFERENCES

1. Chambers, R.J. et al. (Pfizer Products Inc.) *Ether derivs. useful as inhibitors of PDE4 isozymes.* WO 0260896.

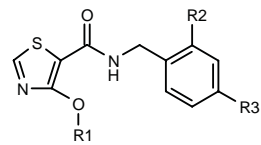
325414

4-(3-Cyanophenoxy)-N-[4-(1-hydroxy-1-methylethyl)benz-yl]thiazole-5-carboxamide



C21 H19 N3 O3 S; Mol wt: 393.4651

ACTION – Phosphodiesterase type 4 (PDE4) inhibitor, potentially useful for the treatment of asthma, chronic bronchitis and chronic obstructive pulmonary disease, among other PDE4-related disorders. Other specifically claimed compounds include the following:



Compound	R1	R2	R3	Formula
325416	1,3-benzodioxol-5-yl	F	CH(Me)2OH	C ₂₁ H ₁₉ FN ₂ O ₅ S
325418	2,1,3-benzothiadiazol-5-yl	H	OCH2CO2H	C ₁₉ H ₁₄ N ₄ O ₅ S ₂
325419	3-NO2-Ph	F	OCH(Me)CO2H	C ₂₀ H ₁₆ FN ₃ O ₇ S
325420	3-NO2-Ph	H	2-CN-PhCONHCH2	C ₂₆ H ₁₉ N ₆ O ₅ S
325422	3-CN-Ph	F	4-CO2H-Ph	C ₂₅ H ₁₆ FN ₃ O ₄ S
325423	3-MeO-Ph	F	4-[CO2HC(Me)2]-Ph	C ₂₈ H ₂₅ FN ₂ O ₅ S
325425	4-F-Ph	F	4-(2-CN-Ph-CONHCH2)-Ph	C ₃₂ H ₂₂ F ₂ N ₄ O ₃ S
325426	3-CN-Ph	H	2-F-4-[5-tetrazolyl-C(Me)2]-Ph	C ₂₈ H ₂₂ FN ₇ O ₂ S

SOURCE – Pfizer.

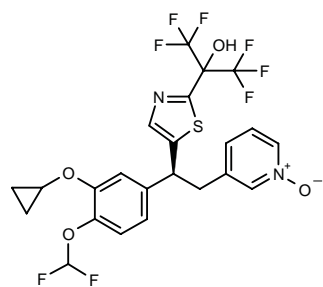
REFERENCES

1. Marfat, A. and McKechney, M.W. (Pfizer Products Inc.) *Thiazolyl-, oxazolyl-, pyrrolyl, and imidazolyl-acid amide derivs. useful as inhibitors of PDE4 isozymes.* WO 0260898.

L-869298

324395

2-[5-[1(S)-[3-(Cyclopropyloxy)-4-(difluoromethoxy)phen-yl]-2-(1-oxidopyridin-3-yl)ethyl]thiazol-2-yl]-1,1,1,3,3,3-hexafluoropropan-2-ol



C23 H18 F8 N2 O4 S; Mol wt: 570.4552

ACTION – Potent phosphodiesterase type 4 (PDE4) inhibitor (IC_{50} = 0.07 μ M in human whole blood) with a long half-life *in vivo* ($t_{1/2}$ = 5 h in rats) and no significant effect on Q-T_c interval (< 4% change) or emetic activity. Potentially useful for the treatment of chronic inflammatory diseases such as asthma and chronic obstructive pulmonary disease (COPD).

SOURCE – Merck Frosst.

REFERENCES

1. Friesen, R. et al. (Merck Frosst Canada Inc.) *Tri-aryl-subst.-ethane PDE4 inhibitors*. US 6399636, WO 0170738.

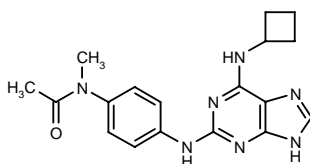
2. Girard, Y. *Discovery of highly potent and well tolerated PDE4 inhibitors*. Drugs Fut 2002, 27(Suppl. A): Abst L13.

NVP-QAB-205*

301070

N-[4-[6-(Cyclobutylamino)-9*H*-purin-2-ylamino]phenyl]-*N*-methylacetamide

QAB-205



C18 H21 N7 O; Mol wt: 351.4119

ACTION – Potent inhibitor of the protein tyrosine kinase Syk (IC_{50} = 9.7 nM) with high selectivity over a panel of tyrosine and serine/threonine kinases including Zap70 and the closely related Lck (IC_{50} = 0.982 and 1.4 μ M, respectively). It displayed good activity in the mast cell degranulation assay (IC_{50} = 90 nM) and showed high bioavailability (70%) in rats after intratracheal administration. Compound inhibited adenosine-induced airways hyperreactivity (ED_{50} = 0.5 mg/kg i.t.) and the acute bronchoconstrictor response to ovalbumin (ED_{50} = 0.1 mg/kg i.t.) in ovalbumin-sensitized Brown Norway rats. Potentially useful for the treatment of asthma.

SOURCE – Novartis.

REFERENCES

1. Collingwood, S.P. et al. (Novartis AG; Novartis-Erfindungen VmbH) *Purine derivs. inhibitors of tyrosine protein kinase syk*. EP 1200435, WO 0109134.

2. Hayler, J. et al. *Novel 2,6-disubstituted purines - The synthesis of potent and selective inhibitors of the protein tyrosine kinase Syk*. Drugs Fut 2002, 27(Suppl. A): Abst P280.

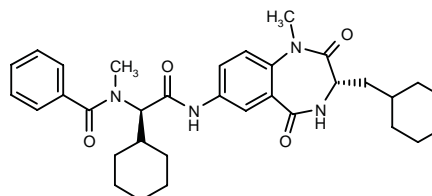
*Identified compound **301070** (see **301064**) Drug Data Rep 2001, 023(07): 0656.

NVP-VAD-463

324388

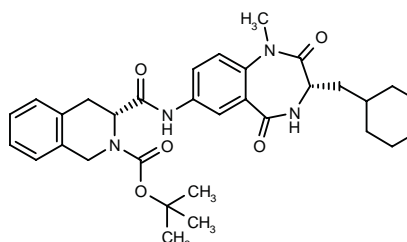
N-[1(*R*)-Cyclohexyl-*N*-[3(*S*)-(cyclohexylmethyl)-1-methyl-2,5-dioxo-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepin-7-yl]carbamoylmethyl]-*N*-methylbenzamide

VAD-463



C33 H42 N4 O4; Mol wt: 558.7188

ACTION – IgE synthesis inhibitor with strong *in vitro* activity in human B-cells and good oral bioavailability in mice (61%). Potentially useful for the treatment of allergic diseases. Another related compound is:



NVP-VAB-053 [324387]: C32 H40 N4 O5
VAB-053

SOURCE – Novartis.

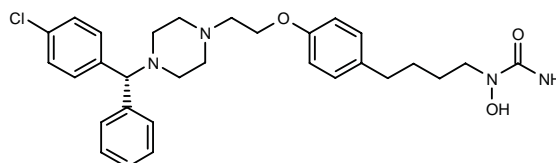
REFERENCES

1. Ettmayer, P. et al. *Potent inhibitors of IgE synthesis in human B-lymphocytes: From a peptidomimetic lead to orally active drug candidates*. Drugs Fut 2002, 27(Suppl. A): Abst C54.

UCB-34743

308373

N-[4-[4-[2-[4-[1(*R*)-(4-Chlorophenyl)-1-phenylmethyl]-piperazin-1-yl]ethoxy]phenyl]butyl]-*N*-hydroxyurea



C30 H37 Cl N4 O3; Mol wt: 537.1003

ACTION – Dual histamine H₁ receptor antagonist (K_i = 83 nM at the human receptor) and 5-lipoxygenase inhibitor (IC_{50} = 191 nM against A23187-induced LTB₄ production in human whole blood) shown to inhibit histamine-induced bronchoconstriction in guinea pigs (57-73% inhibition at 2 mg/kg p.o. at 1-6 h) and LTB₄ production in blood (70-94% inhibition at 1-6 h). In sensitized guinea pigs, a dose of 2 mg/kg p.o. abolished both early and late bronchoconstrictor responses to antigen challenge. Potentially useful for the treatment of asthma and allergic rhinitis.

SOURCE – UCB.

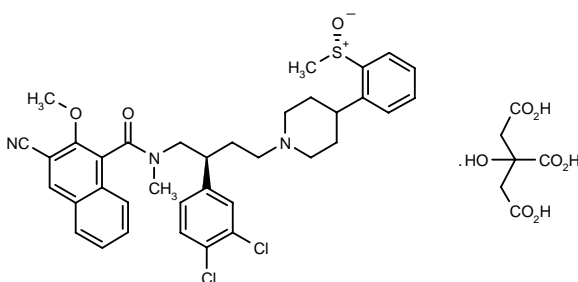
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1. Scannel, R. et al. (UCB SA) *Cpds. and methods for treatment of asthma, allergy and inflammatory disorders*. US 6451801, WO 0058295.
2. Ellis, J.L. et al. *Ucb 34743, a novel anti-inflammatory agent possessing both H1 antagonist and 5-lipoxygenase inhibitory activity*. *Inflamm Res* 2001, 50(Suppl. 3): Abst W22/02.
3. Scannell, R.T. et al. *The design and synthesis of a novel series of dual acting molecules possessing 5-lipoxygenase enzyme inhibition and histamine H1 receptor antagonist properties*. *Drugs Fut* 2002, 27(Suppl. A): Abst C56.

ZD-4974*

288461

3-Cyano-*N*-[2-(*S*)-(3,4-dichlorophenyl)-4-[4-[2-[(*S*)-methylsulfinyl]phenyl]piperidin-1-yl]butyl]-2-methoxy-*N*-methylnaphthalene-1-carboxamide citrate



C36 H37 Cl2 N3 O3 S . C6 H8 O7; Mol wt: 854.8005

ACTION – Potent and selective tachykinin NK₁ receptor antagonist (K_i = 0.17, 67 and 220 nM for human NK₁, NK₂ and NK₃ receptors, respectively) with a pK_B value of 9.50 for inhibition of NK₁-induced rabbit pulmonary artery contractions. *In vivo*, it inhibited NK₁-induced lung plasma protein extravasation with an ED₅₀ value of 0.07 μ mol/kg p.o. while displaying 30-fold weaker potency against the NK₂ agonist-induced increase in airways resistance. Potentially useful for the treatment of asthma.

SOURCE – AstraZeneca.

REFERENCES

1. Bernstein, P.R. et al. (AstraZeneca plc) *Naphthalenecarboxamides as tachykinin receptor antagonists*. EP 1119551, WO 0020389.
2. Rumsey, W.L. and Furr, B.J.A. (AstraZeneca AB) *Pharmaceutical combination of neurokinin receptor antagonist and proton pump inhibitor*. WO 0069438.
3. Albert, J.S. et al. *Design, synthesis, and SAR of tachykinin antagonists: Modulation of balance in NK1/NK2 receptor antagonist activity*. *J Med Chem* 2002, 45(18): 3972.
4. Ghanekar, S. et al. *Pharmacological analysis of antagonists' binding to human tachykinin NK1 and NK2 receptors*. *Soc Neurosci Abst* 2001, 27: Abst 149.20.
5. Logue, S.F. et al. *Guinea pigs in anxiety and depression models: Evaluation of NK1 antagonists*. *Soc Neurosci Abst* 2001, 27: Abst 336.5.

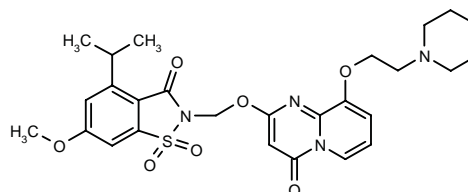
*Identified compound **288461** (see **288460**) Drug Data Rep 2000, 022(07): 0598.

TREATMENT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

SSR-69071

306867

2-(4-Isopropyl-6-methoxy-1,1,3-trioxo-2,3-dihydro-1,2-benzisothiazol-2-ylmethoxy)-9-[2-(1-piperidinyl)ethoxy]-4*H*-pyrido[1,2-*a*]pyrimidin-4-one



C27 H32 N4 O7 S; Mol wt: 556.6368

ACTION – Potent, selective, and orally active human leukocyte elastase (HLE) inhibitor (K_i = 0.017 nM) that acts as a slow, tight-binding inhibitor. It showed selectivity relative to HLE from other species (K_i = 1.70, 3.01 and 58 nM against mouse, rat and rabbit HLE, respectively), as well as over a range of other receptors and enzymes. It inhibited HLE activity in bronchoalveolar lavage fluid for at least 4 h after oral administration to mice and HLE-induced lung hemorrhage with an ED₅₀ of 2.6 mg/kg p.o. Potentially useful for the treatment of chronic obstructive pulmonary diseases (COPD), asthma, emphysema and cystic fibrosis.

SOURCE – Sanofi-Synthélabo.

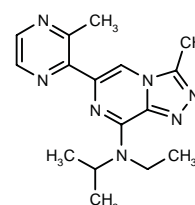
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1. Arányi, P. et al. (Sanofi-Synthélabo) *Saccharin derivs. as orally active elastase inhibitors*. WO 0144245.
2. Varga, M. et al. *A novel orally active inhibitor of HLE*. *Drugs Fut* 2002, 27(Suppl. A): Abst C57.
3. *R&D portfolio*. Sanofi-Synthelabo Web Site 2001, Aug 31.
4. *R&D portfolio*. Sanofi-Synthelabo Web Site 2002, March 1.

UK-399276

324389

N-Ethyl-*N*-isopropyl-3-methyl-6-(3-methylpyrazin-2-yl)[1,2,4]triazolo[4,3-*a*]pyrazin-8-amine



C16 H21 N7; Mol wt: 311.3909

ACTION – Potent nonredox inhibitor of 15-lipoxygenase (15-LO) isozyme a ($K_i = 8.3$ nM) with good selectivity versus cyclooxygenase type 1 (COX-1) and 12-lipoxygenase. Potentially useful for reducing mucus hypersecretion in chronic bronchitis.

SOURCE – Pfizer.

REFERENCES

1. Brown, A. et al. *Identification and optimisation of non-redox inhibitors of 15-lipoxygenase-a*. *Drugs Fut* 2002, 27(Suppl. A): Abst C55.

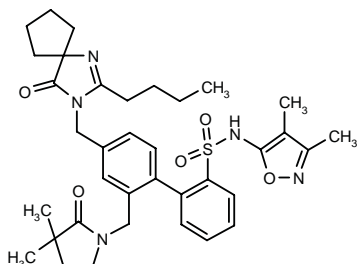
CARDIOVASCULAR DRUGS

ANTIHYPERTENSIVE DRUGS

BMS-248360

324487

4'-(2-Butyl-4-oxo-1,3-diazaspiro[4.4]-1-nonen-3-ylmethyl)-N-(3,4-dimethylisoxazol-5-yl)-2'-(3,3-dimethyl-2-oxopyrrolidin-1-ylmethyl)biphenyl-2-sulfonamide



C36 H45 N5 O5 S; Mol wt: 659.8475

ACTION – Dual-acting angiotensin II AT_1 and endothelin ET_A receptor antagonist with excellent affinity for human and rat AT_1 ($K_i = 10$ and 6.0 nM, respectively) and human ET_A receptors ($K_i = 1.9$ nM), while having no activity at AT_2 or ET_B receptors ($K_i > 10$ μ M). Compound exhibited good oral bioavailability in rats (38%), high plasma levels after oral administration ($C_{max} = 3.1$ μ M) and a favorable elimination profile. In conscious normotensive rats, it inhibited both the angiotensin II- and big ET-1-induced pressor responses following oral ($ED_{50} = 39$ and 26 μ mol/kg, respectively) and i.v. administration ($ED_{50} = 1.4$ and 2.1 μ mol/kg, respectively). Potentially useful for the treatment of hypertension.

SOURCE – Bristol-Myers Squibb.

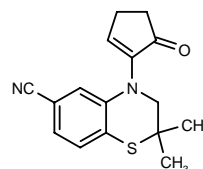
REFERENCES

1. Murugesan, N. et al. (Bristol-Myers Squibb Co.) *Biphenyl sulfonamides as dual angiotensin endothelin receptor antagonists*. EP 1094816, WO 0001389.
2. Murugesan, N. et al. (Bristol-Myers Squibb Co.) *Biphenyl sulfonamides as dual angiotensin endothelin receptor antagonists*. EP 1237888, WO 0144239.
3. Murugesan, N. et al. *Discovery of N-isoxazolyl biphenylsulfonamides as potent dual angiotensin II and endothelin A receptor antagonists*. *J Med Chem* 2002, 45(18): 3829.

KOCN-7

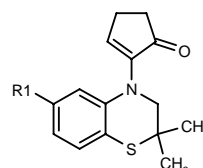
324565

2,2-Dimethyl-4-(5-oxo-1-cyclopenten-1-yl)-3,4-dihydro-2H-1,4-benzothiazine-6-carbonitrile



C16 H16 N2 O S; Mol wt: 284.3814

ACTION – Potent potassium channel activator with strong vasodilating activity in rat aortic rings ($pIC_{50} = 11.73$) and 10,000-fold higher potency compared to cromakalim. Potentially useful for the treatment of hypertension and angina. Other related compounds are:



Compound	R1	Formula
KONO-7 [324564]	NO2	C ₁₅ H ₁₆ N ₂ O ₃ S
KOCF-7 [324566]	CF3	C ₁₆ H ₁₆ F ₃ NOS

SOURCES – Università degli Studi di Perugia, Perugia (IT); Università degli Studi di Pisa, Pisa (IT).

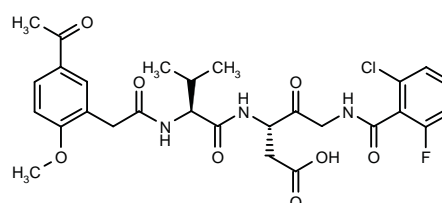
REFERENCES

1. Cecchetti, V. et al. *Highly potent KATP channel activators*. *Drugs Fut* 2002, 27(Suppl. A): Abst P451.

TREATMENT OF DISORDERS OF THE CORONARY ARTERIES AND ATHEROSCLEROSIS

322977

3(S)-[N-[2-(5-Acetyl-2-methoxyphenyl)acetyl]-L-valyl-amino]-5-(2-chloro-6-fluorobenzamido)-4-oxopentanoic acid



C28 H31 Cl F N3 O8; Mol wt: 592.0169

ACTION – Peptidomimetic compound with the ability to inhibit caspase 3, potentially useful for the treatment of cardiac and cerebral ischemia, reperfusion injury, sepsis and bacterial meningitis. Other specifically claimed γ -ketoacid dipeptide derivatives include the following:

ACTION – Potent nonredox inhibitor of 15-lipoxygenase (15-LO) isozyme a ($K_i = 8.3$ nM) with good selectivity versus cyclooxygenase type 1 (COX-1) and 12-lipoxygenase. Potentially useful for reducing mucus hypersecretion in chronic bronchitis.

SOURCE – Pfizer.

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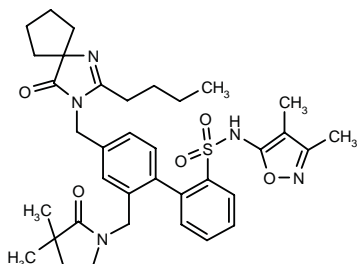
CARDIOVASCULAR DRUGS

ANTIHYPERTENSIVE DRUGS

BMS-248360

324487

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SOURCE – Bristol-Myers Squibb.

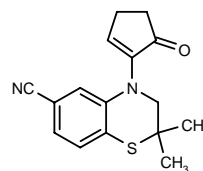
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KOCN-7

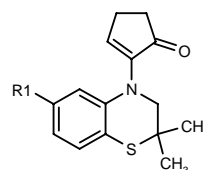
324565

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KOCF-7 [324566]	CF3	C ₁₆ H ₁₆ F ₃ NOS

SOURCES – Università degli Studi di Perugia, Perugia (IT); Università degli Studi di Pisa, Pisa (IT).

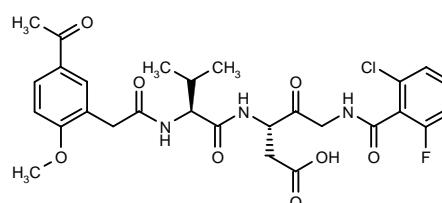
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TREATMENT OF DISORDERS OF THE CORONARY ARTERIES AND ATHEROSCLEROSIS

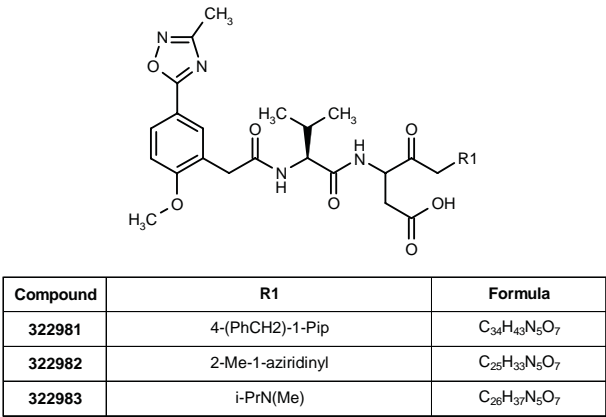
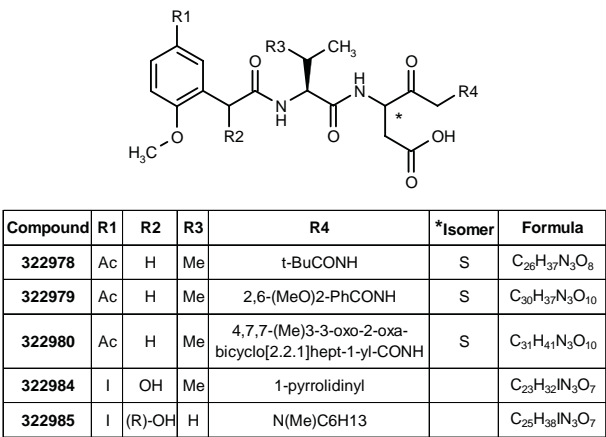
322977

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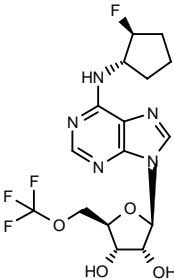
SOURCE – Merck Frosst.

REFERENCES

1. Han, Y. et al. (Merck Frosst Canada Inc.) *γ-Ketoacid dipeptide derivs. as inhibitors of caspase-3*. WO 0248179.

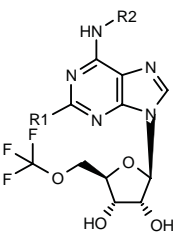
323108

N⁶-[(1*S*,2*S*)-2-Fluorocyclopentyl]-5'-*O*-(trifluoromethyl)-adenosine



C16 H19 F4 N5 O4; Mol wt: 421.3491

ACTION – Adenosine A₁ receptor agonist with potency comparable to the nonselective agonist *N*-ethylcarbox-amidoadenosine (NECA), while exhibiting increased selectivity over A₃ receptors. Potentially useful for the treatment of ischemic heart disease, peripheral vascular disease, stroke, pain, convulsions and epilepsy. Other exemplified adenosine analogues are:



Compound	R1	R2	Formula
323109	H	CH2CH2SO2NHMe	C14H19F3N6O6S
323111	H	tetrahydro-4-thiopyranyl	C16H20F3N5O4S
323112	H	3,4-(F)2-Ph	C17H14F5N5O4
323114	H	1,1-dioxo-tetrahydro-4-thiopyranyl	C16H20F3N5O6S
323115	H	t-Bu	C15H20F3N5O4
323117	H	1-CO2Et-4-Pip	C19H25F3N6O6
323118	H	(1 <i>S</i> ,2 <i>S</i>)-2-OH-cyclopentyl	C16H20F3N5O5
323119	H	CH2CH(OH)CH2OH	C14H18F3N5O6
323120	H	3(R)-THF	C15H18F3N5O5
323121	H	3(S)-THF	C15H18F3N5O5
323122	H	CH2CH2NHAc	C15H19F3N6O5
323124	CH3	1-CO2Et-4-Pip	C19H25F3N6O6

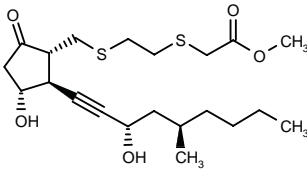
SOURCE – GlaxoSmithKline.

REFERENCES

1. Box, P.C. et al. (GlaxoSmithKline Inc.) *Adenosine analogues and related method of treatment*. US 6407076, WO 9924450.

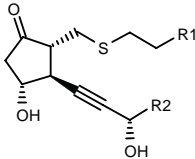
324431

17(*R*),20-Dimethyl-13,14-didehydro-3,6-dithiaprosta-glandin E₁ methyl ester



C21 H34 O5 S2; Mol wt: 430.6266

ACTION – Prostaglandin E₁ derivative able to inhibit the proliferation of smooth muscle cells, and thus having potential in the treatment of restenosis following PTCA. Compound almost completely inhibited the proliferation of human vascular smooth muscle cells *in vitro* at 10 μM. Other exemplified compounds are:



Compound	R1	R2	Formula
324432	CH2CH2CO2H	cyclohexyl	C20H30O5S
324433	CH2CO2Me	cyclohexyl	C20H30O5S
324434	CH2CO2Me	(R)-CH2CH(Me)Bu	C21H34O5S
324435	SCH2CO2Me	cyclohexyl	C20H30O5S2

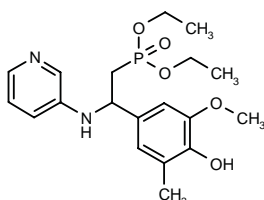
SOURCE – Taisho.

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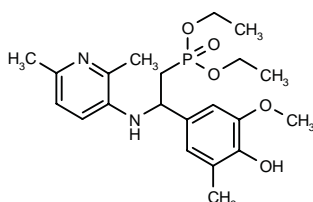
324765

2-(4-Hydroxy-3-methoxy-5-methylphenyl)-2-(pyridin-3-ylamino)ethylphosphonic acid diethyl ester



C19 H27 N2 O5 P; Mol wt: 394.4053

ACTION – Lipoprotein(a) (Lp[a])-lowering agent able to decrease apoprotein(a) levels in monkey hepatocytes (17% reduction at 20 μ M) and plasma Lp(a) levels in monkeys by 52% at 25 mg/kg/day p.o. for 4 weeks. Potentially useful for the treatment of atherosclerosis and thrombosis. Another related compound is:



324766: C21 H31 N2 O5 P

SOURCES – GlaxoSmithKline; Ilex Oncology.

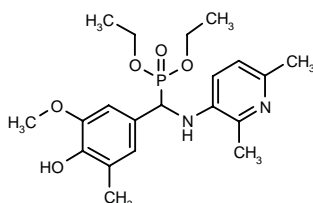
REFERENCES

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SR-103912*

268703

1-(2,6-Dimethylpyridin-3-ylamino)-1-(4-hydroxy-3-methoxy-5-methylphenyl)methylphosphonic acid diethyl ester



C20 H29 N2 O5 P; Mol wt: 408.4321

ACTION – Potent plasma lipoprotein(a) (Lp[a])-lowering agent, a β -aminoethylphosphonate potentially useful for the prevention of coronary heart and peripheral vascular diseases.

SOURCES – GlaxoSmithKline; Ilex Oncology.

REFERENCES

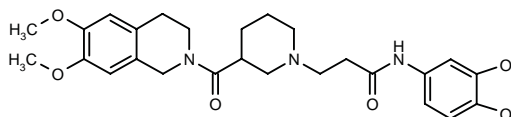
1. Nguyen, L.M. et al. (Symphar S.A.; SmithKline Beecham plc) *Pharmaceutical aminophosphonic acid derivs.* EP 0946572, US 6303784, WO 9828310.
2. Phan, H.T. et al. *Synthesis of a new series of compounds with lipoprotein(a)-lowering activity, Part 4: α -Substituted- β -amino-ethylphosphonates.* Drugs Fut 2002, 27(Suppl. A): Abst P398.

*Identified compound **268703** (see **268702**) Drug Data Rep 1998, 020(10): 0856.

YM-193489*

298566

N-(1,3-Benzodioxol-5-yl)-3-[3-(6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-ylcarbonyl)piperidin-1-yl]propionamide



C27 H33 N3 O6; Mol wt: 495.5727

ACTION – Bradycardic agent able to decrease the spontaneous beating rate in guinea pig atria with an EC_{30} value of 0.3 μ M. In rats, compound reduced heart rate by 46.2% at a dose of 3 mg/kg i.v., and both isomers of the compound showed 3-fold higher bradycardic activity than zatebradine following oral administration, while having no effect on blood pressure. Potentially useful for the prevention of cardiac mortality in patients with ischemic heart disease and congestive heart failure.

SOURCE – Yamanouchi.

REFERENCES

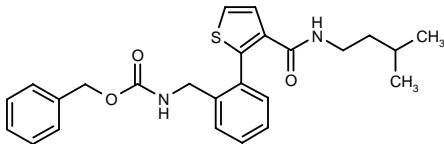
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*Identified compound **298566** Drug Data Rep 2001, 023(05): 0456.

ANTIARRHYTHMIC DRUGS

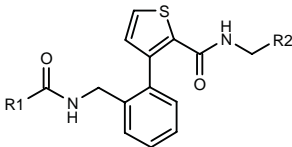
323212

N-[2-[3-[N-(3-Methylbutyl)carbamoyl]thien-2-yl]benzyl]-carbamic acid benzyl ester

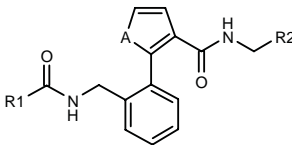


C25 H28 N2 O3 S; Mol wt: 436.5732

ACTION – Potassium Kv1.5 channel blocker (IC₅₀ = 1.2 μM against human Kv1.5 channels expressed in *Xenopus* oocytes), potentially useful for the treatment of arrhythmias including supraventricular arrhythmia, atrial fibrillation, atrial flutter and reentry arrhythmia. Other exemplified compounds are:



Compound	R1	R2	Formula
323213	OCH2Ph	2,4-(F)2-Ph	C ₂₇ H ₂₂ F ₂ N ₂ O ₃ S
323216	4-MeO-PhCH2	i-Bu	C ₂₆ H ₃₀ N ₂ O ₃ S
323217	4-MeO-PhCH2	2,4-(F)2-Ph	C ₂₈ H ₂₄ F ₂ N ₂ O ₃ S



Compound	R1	R2	A	Formula
323214	OCH2Ph	2,4-(F)2-Ph	S	C ₂₇ H ₂₂ F ₂ N ₂ O ₃ S
323215	OCH2Ph	i-Bu	O	C ₂₅ H ₂₈ N ₂ O ₄
323218	4-MeO-PhCH2	i-Bu	S	C ₂₆ H ₃₀ N ₂ O ₃ S
323219	4-MeO-PhCH2	2,4-(F)2-Ph	S	C ₂₈ H ₂₄ F ₂ N ₂ O ₃ S

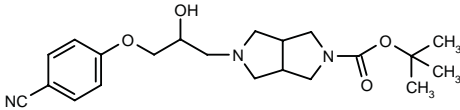
SOURCE – Aventis Pharma.

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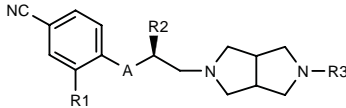
325367

5-[3-(4-Cyanophenoxy)-2-hydroxypropyl]perhydropyrrolo-[3,4-c]pyrrole-2-carboxylic acid *tert*-butyl ester



C21 H29 N3 O4; Mol wt: 387.4771

ACTION – Class III antiarrhythmic agent, potentially useful for the treatment of cardiac arrhythmias, particularly atrial and ventricular arrhythmias. Other exemplified compounds include the following:



Compound	R1	R2	R3	A	Formula
325368	H	OH	4-Me-PhSO2NHCO	-OCH2-	C ₂₄ H ₂₈ N ₄ O ₅ S
325370	H	H	3,4-(F)2-PhNHCO	-NHCH2-	C ₂₃ H ₂₅ F ₂ N ₅ O
325373	H	H	4-(CF3S)-PhNHCO	-SO2CH2-	C ₂₄ H ₂₅ F ₃ N ₄ O ₃ S ₂
325375	CN	H	CONHEt	-O-	C ₁₉ H ₂₃ N ₅ O ₂
325378	H	OH	CO2(CH2)3SO2Me	-OCH2-	C ₂₁ H ₂₉ N ₃ O ₆ S
325379	H	H	CO2Et	-O-	C ₁₈ H ₂₃ N ₃ O ₃
325380	H	H	CO2CH2CH2OMe	-SO2CH2-	C ₂₀ H ₂₇ N ₃ O ₅ S
325381	H	H	CH2CH2OCH2CH2OMe	-NHCH2-	C ₂₁ H ₃₂ N ₄ O ₂
325383	H	NH2	4-Ac-1-Piz-(CH2)3	-OCH2-	C ₂₅ H ₃₈ N ₆ O ₂

SOURCE – AstraZeneca.

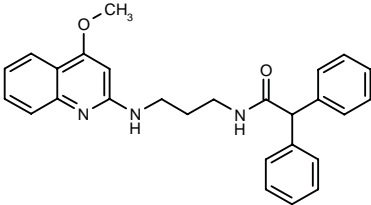
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HEART FAILURE THERAPY

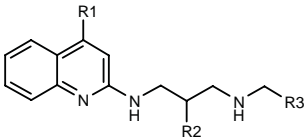
324934

N-[3-(4-Methoxyquinolin-2-ylamino)propyl]-2,2-diphenyl-acetamide



C27 H27 N3 O2; Mol wt: 425.5293

ACTION – Urotensin-II receptor antagonist (K_i = 90 nM), potentially useful for the treatment of congestive heart failure, stroke, ischemic heart disease, cardiac arrhythmia, hypertension, chronic obstructive pulmonary disease, restenosis, asthma, neurogenic inflammation, metabolic vasculopathies, drug abuse, schizophrenia, impulsivity, anxiety, stress, depression, neuromuscular function disorders and diabetes. Other specifically claimed compounds are:



Compound	R1	R2	R3	Formula
324935	OMe	H	1-(PhCH2)-3-indolyl	C ₂₉ H ₃₀ N ₄ O
324936	CON(Me)2	H	4-Cl-3-CF3-Ph	C ₂₃ H ₂₄ ClF ₃ N ₄ O
324937	CONHMe	H	4-Cl-3-CF3-Ph	C ₂₂ H ₂₂ ClF ₃ N ₄ O
324938	OMe	Pr	1-(PhCH2)-3-indolyl	C ₃₂ H ₃₆ N ₄ O
324939	OMe	Ph	1-(PhCH2)-3-indolyl	C ₃₅ H ₃₄ N ₄ O
324940	OMe	H	1-(PhSO2)-3-indolyl	C ₂₈ H ₂₈ N ₄ O ₃ S
324941	OMe	Me	1-(PhCH2)-3-indolyl	C ₃₀ H ₃₂ N ₄ O

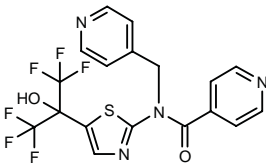
SOURCE – GlaxoSmithKline.

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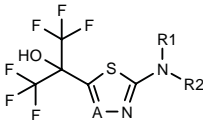
325174

N-(Pyridin-4-ylmethyl)-*N*-[5-[2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl]thiazol-2-yl]pyridine-4-carboxamide

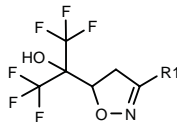


C18 H12 F6 N4 O2 S; Mol wt: 462.3728

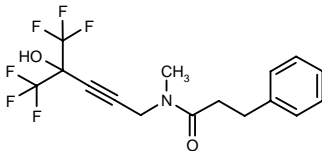
ACTION – Malonyl-CoA decarboxylase (MCD) inhibitor (IC_{50} = 0.024 μ M), considered to have potential in the treatment of cardiovascular disorders such as congestive heart failure and angina pectoris, as well as diabetes, obesity, acidosis and cancer. Other exemplified compounds are:



Compound	R1	R2	A	Formula
325175	Ac	Bu	CH	C ₁₂ H ₁₄ F ₆ N ₂ O ₂ S
325176	CONHEt	Bu	CH	C ₁₃ H ₁₇ F ₆ N ₃ O ₂ S
325177	CHO	4-Pyr-CH2	CH	C ₁₃ H ₉ F ₆ N ₃ O ₂ S
325178	4-Cl-PhSO2	H	CH	C ₁₂ H ₇ ClF ₆ N ₂ O ₃ S ₂
325179	i-PrCO	Et	N	C ₁₁ H ₁₃ F ₆ N ₃ O ₂ S



Compound	R1	Formula
325181	CONHCH(Me)C5H11	C ₁₄ H ₂₀ F ₆ N ₂ O ₃
325182	CON(i-Pr)2	C ₁₃ H ₁₈ F ₆ N ₂ O ₃
325183	1-pyrrolidinyl	C ₁₀ H ₁₂ F ₆ N ₂ O ₂
325184	4-Me-Ph	C ₁₃ H ₁₁ F ₆ NO ₂



325180: C16 H15 F6 N O2

SOURCE – Chugai.

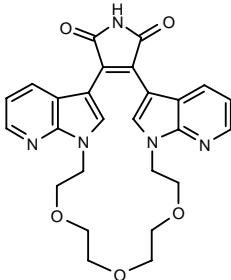
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MISCELLANEOUS CARDIOVASCULAR DRUGS

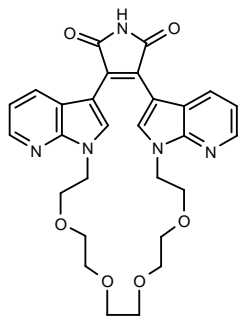
322699

7,9,10,12,13,15,16,23,24,25-Decahydro-6*H*-5,26:17,22-dimethenodipyrido[2,3-*k*:3',2'-*q*]pyrrolo[3,4-*n*]-[1,4,7,10,19]trioxadiazacyclohenicosine-23,25-dione



C26 H25 N5 O5; Mol wt: 487.5135

ACTION – Kinase inhibitor particularly active against protein kinase C (PKC- α , PKC- β 2 and PKC- γ subtypes) and/or glycogen synthase kinase GSK-3 β . Potentially useful for the treatment of a variety of cardio-vascular disorders, diabetes and diabetic complications, inflammatory and immune diseases, dermatological disorders, cancer and CNS disorders. Another exemplified macroheterocyclic compound is:



322702: C28 H29 N5 O6

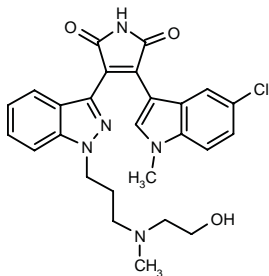
SOURCE – Ortho-McNeil.

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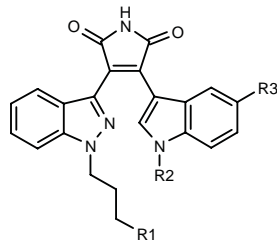
322703

3-(5-Chloro-1-methyl-1*H*-indol-3-yl)-4-[1-[3-[*N*-(2-hydroxyethyl)-*N*-methylamino]propyl]-1*H*-indazol-3-yl]-2,5-dihydro-1*H*-pyrrole-2,5-dione



C26 H26 Cl N5 O3; Mol wt: 491.9764

ACTION – Kinase inhibitor particularly active against protein kinase C (PKC- α , PKC- β 2 and PKC- γ subtypes) and glycogen synthase kinase GSK-3 β , with respective IC₅₀ values of 0.007, 0.065, 0.074 and 0.014 μ M. Potentially useful for the treatment of a variety of cardiovascular disorders, diabetes and diabetic complications, inflammatory and immune diseases, dermatological disorders, cancer and CNS disorders. Other exemplified indazolyl-substituted pyrrole compounds are:



Compound	R1	R2	R3	Formula
322704	N(Me)2	Et	Cl	C ₂₆ H ₂₆ ClN ₅ O ₂
322705	4-morpholinyl	Et	H	C ₂₈ H ₂₉ N ₅ O ₃
322706	1-pyrrolidinyl	Me	Cl	C ₂₇ H ₂₆ ClN ₅ O ₂
322707	4-Me-1-PiZ	Me	Cl	C ₂₈ H ₂₉ ClN ₅ O ₂
322708	4-morpholinyl	Me	Cl	C ₂₇ H ₂₆ ClN ₅ O ₃
322709	NHMe	Me	Cl	C ₂₄ H ₂₂ ClN ₅ O ₂
322710	OH	3-Pyr	H	C ₂₇ H ₂₁ N ₅ O ₃
322711	OH	3-quinolyl	H	C ₃₁ H ₂₃ N ₅ O ₃
322712	N(Me)CH2CH2OH	3-Pyr	H	C ₃₀ H ₂₈ N ₆ O ₃
322713	OMe	3-Pyr	H	C ₂₈ H ₂₉ N ₅ O ₃

SOURCE – Ortho-McNeil.

REFERENCES

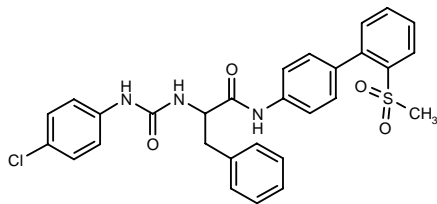
1. Zhang, H.-C. et al. (Ortho-McNeil Pharmaceutical, Inc.) *Indazolyl-substd. pyrroline cpds. as kinase inhibitors*. WO 0246183.

AGENTS AFFECTING BLOOD COAGULATION

ANTICOAGULANTS

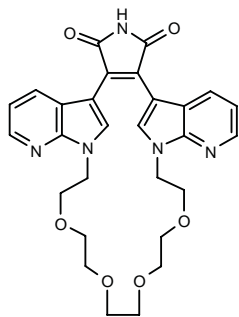
323086

*N*²-[*N*-(4-Chlorophenyl)carbamoyl]-*N*¹-[2'-(methylsulfonyl)biphenyl-4-yl]-D,L-phenylalaninamide



C29 H26 Cl N3 O4 S; Mol wt: 548.0604

ACTION – Anticoagulant that acts by inhibiting factor Xa and factor VIIa (IC₅₀ = 86 and 65 nM, respectively). Potentially useful for the treatment of coagulation disorders including thrombosis, myocardial infarction, arteriosclerosis, inflammation, stroke, angina pectoris, postangioplasty restenosis, intermittent claudication and cancer. Another exemplified compound is:



322702: C28 H29 N5 O6

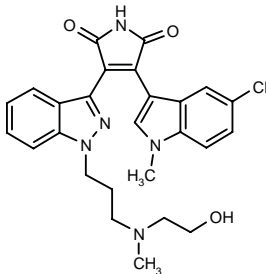
SOURCE – Ortho-McNeil.

REFERENCES

1. Kuo, G.-H. et al. (Ortho-McNeil Pharmaceutical, Inc.) *Macroheterocyclic cpds. useful as kinase inhibitors*. WO 0246197.

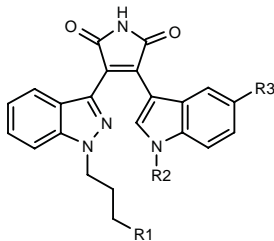
322703

3-(5-Chloro-1-methyl-1*H*-indol-3-yl)-4-[1-[3-[*N*-(2-hydroxyethyl)-*N*-methylamino]propyl]-1*H*-indazol-3-yl]-2,5-dihydro-1*H*-pyrrole-2,5-dione



C26 H26 Cl N5 O3; Mol wt: 491.9764

ACTION – Kinase inhibitor particularly active against protein kinase C (PKC- α , PKC- β 2 and PKC- γ subtypes) and glycogen synthase kinase GSK-3 β , with respective IC₅₀ values of 0.007, 0.065, 0.074 and 0.014 μ M. Potentially useful for the treatment of a variety of cardiovascular disorders, diabetes and diabetic complications, inflammatory and immune diseases, dermatological disorders, cancer and CNS disorders. Other exemplified indazolyl-substituted pyrrole compounds are:



Compound	R1	R2	R3	Formula
322704	N(Me)2	Et	Cl	C ₂₆ H ₂₆ ClN ₅ O ₂
322705	4-morpholinyl	Et	H	C ₂₈ H ₂₉ N ₅ O ₃
322706	1-pyrrolidinyl	Me	Cl	C ₂₇ H ₂₆ ClN ₅ O ₂
322707	4-Me-1-PiZ	Me	Cl	C ₂₈ H ₂₉ ClN ₅ O ₂
322708	4-morpholinyl	Me	Cl	C ₂₇ H ₂₆ ClN ₅ O ₃
322709	NHMe	Me	Cl	C ₂₄ H ₂₂ ClN ₅ O ₂
322710	OH	3-Pyr	H	C ₂₇ H ₂₁ N ₅ O ₃
322711	OH	3-quinolyl	H	C ₃₁ H ₂₃ N ₅ O ₃
322712	N(Me)CH2CH2OH	3-Pyr	H	C ₃₀ H ₂₈ N ₆ O ₃
322713	OMe	3-Pyr	H	C ₂₈ H ₂₉ N ₅ O ₃

SOURCE – Ortho-McNeil.

REFERENCES

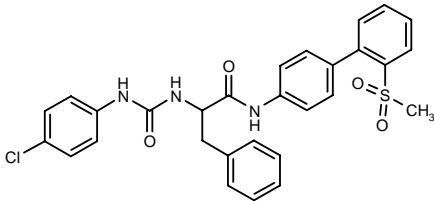
1. Zhang, H.-C. et al. (Ortho-McNeil Pharmaceutical, Inc.) *Indazolyl-substd. pyrroline cpds. as kinase inhibitors*. WO 0246183.

AGENTS AFFECTING BLOOD COAGULATION

ANTICOAGULANTS

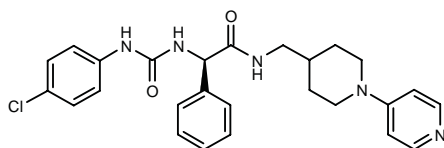
323086

*N*²-[*N*-(4-Chlorophenyl)carbamoyl]-*N*¹-[2'-(methylsulfonyl)biphenyl-4-yl]-D,L-phenylalaninamide



C29 H26 Cl N3 O4 S; Mol wt: 548.0604

ACTION – Anticoagulant that acts by inhibiting factor Xa and factor VIIa (IC₅₀ = 86 and 65 nM, respectively). Potentially useful for the treatment of coagulation disorders including thrombosis, myocardial infarction, arteriosclerosis, inflammation, stroke, angina pectoris, postangioplasty restenosis, intermittent claudication and cancer. Another exemplified compound is:



323087: C26 H28 Cl N5 O2

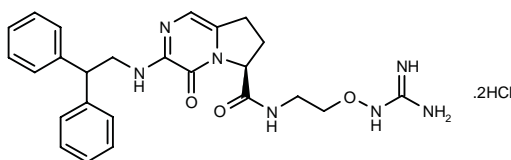
SOURCE – Merck KGaA.

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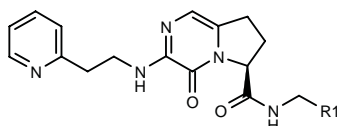
323089

3-(2,2-Diphenylethylamino)-*N*-[2-(guanidinoxy)ethyl]-4-oxo-4,6,7,8-tetrahydropyrrolo[1,2-*a*]pyrazine-6(*S*)-carboxamide dihydrochloride



C₂₅ H₂₉ N₇ O₃ . 2HCl; Mol wt: 548.4719

ACTION – Anticoagulant, an inhibitor of trypsin-related serine proteases, particularly thrombin, giving a CT2 value (concentration required to double coagulation time) of 0.10 μ M in coagulation assays using human plasma. Other exemplified compounds are:



Compound	R1	Formula
323090	4-[NH2C(=NOH)]-Ph	C ₂₃ H ₂₆ N ₇ O ₃
323092	2-(4,5-dihydro-1H-imidazol-2-yl-CH ₂ O)-Ph	C ₂₆ H ₂₈ N ₇ O ₃
323093	6-indolyl	C ₂₄ H ₂₄ N ₆ O ₂

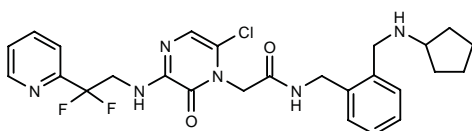
SOURCE – Servier.

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324668

2-[6-Chloro-3-[2,2-difluoro-2-(2-pyridyl)ethylamino]-2-oxo-1,2-dihydropyrazin-1-yl]-*N*-[2-(cyclopentylaminomethyl)-benzyl]acetamide



C26 H29 Cl F2 N6 O2: Mol wt: 531.0041

ACTION – Thrombin inhibitor, potentially useful for the treatment of thromboembolic disorders such as venous thromboembolism, pulmonary embolism, deep venous thrombosis and thromboembolic stroke.

SOURCE – Merck & Co.

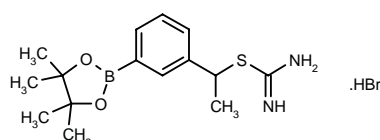
REFERENCES

1. Selnick, H.G. et al. (Merck & Co., Inc.) *Thrombin inhibitors*. WO 0257225.

TRI-974

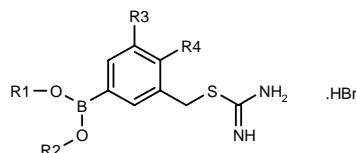
324610

S-[1-[3-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-phenyl]ethyl]isothiourea hydrobromide



C15 H23 B N2 O2 S . HBr; Mol wt: 387.1476

ACTION – Inhibitor of trypsin-like serine proteases that demonstrated *in vitro* activity against factor IXa, thrombin, trypsin, factor Xa, plasmin and urokinase. Potentially useful for the treatment of thrombosis, cancer, angiogenesis and restenosis. Other exemplified compounds are:



Compound	R1	R2	R3	R4	Formula
TRI-967 [324613]	H	H	Me	H	C ₉ H ₁₃ BN ₂ O ₂ S.HBr
TRI-1055 [324618]	-C(Me) ₂ C(Me)-		H	OPh	C ₂₀ H ₂₅ BN ₂ O ₃ S.HBr
TRI-1069 [324619]	H	H	H	3-CN-PhO	C ₁₈ H ₁₄ BN ₃ O ₃ S.HBr

SOURCE – Trigen.

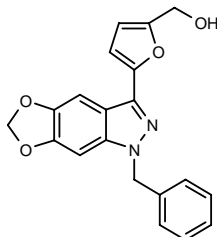
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1. Deadman, J.J. et al. (Trigen Ltd.) *Serine protease inhibitors comprising a hydrogen-bond acceptor*. WO 0257273.

ANTIPLATELET THERAPY

324849

1-[5-(1-Benzyl-1*H*-[1,3]dioxolo[4,5-*f*]indazol-3-yl)furan-2-yl]methanol



C20 H16 N2 O4; Mol wt: 348.3564

ACTION – A representative compound from a series of fused pyrazole derivatives with the ability to increase intracellular levels of cGMP, through either activation of soluble guanylate cyclase (sGC) or inhibition of phosphodiesterase (PDE). *In vitro*, it demonstrated sGC-activating and PDE-inhibitory activity. It also prevented platelet aggregation induced by thrombin, arachidonic acid, collagen and PAF. Potentially useful for the treatment of atherosclerosis, myocardial infarction, unstable angina, thrombosis and hypertension, as well as erectile dysfunction.

SOURCE – Yung Shin.

REFERENCES

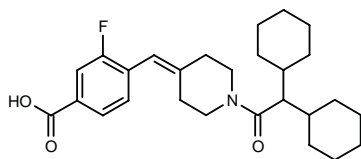
1. Sheng-Chu, K. et al. (Yung Shin Pharm. Ind. Co. Ltd.) *Fused pyrazolyl cpds*. EP 1227099.

RENAL-UROLOGIC DRUGS

BENIGN PROSTATIC HYPERPLASIA THERAPY

322889

4-[1-(2,2-Dicyclohexylacetyl)piperidin-4-ylidenemethyl]-3-fluorobenzoic acid



C27 H36 F N O3; Mol wt: 441.5834

ACTION – Potent and selective steroid 5 α -reductase type 2 inhibitor (IC_{50} = 0.011 and 3 μ M against human and rat enzyme, respectively) able to reverse the trophic effect of testosterone on castrated rat prostate (47% inhibition at 11.8 mg/kg s.c.). Potentially useful for the treatment of benign prostatic hyperplasia.

SOURCE – Universität des Saarlandes, Saarbrücken (DE).

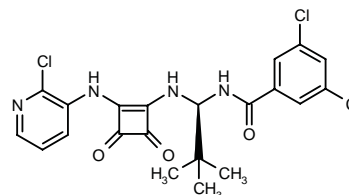
REFERENCES

1. Picard, F. et al. *Synthesis and evaluation of 2'-substituted 4-(4'-carboxy- or 4'-carboxymethylbenzylidene)-N-acylpiperidines: Highly potent and in vivo active steroid 5 α -reductase type 2 inhibitors*. J Med Chem 2002, 45(16): 3406.
2. Picard, F. et al. *Synthesis and evaluation of N-acyl-4-benzylidenepiperidines: Highly potent and in vivo active steroid-5 α -reductase type 2 inhibitors*. Drugs Fut 2002, 27(Suppl. A): Abst P425.

TREATMENT OF URINARY INCONTINENCE

323846

3,5-Dichloro-*N*-[1(*S*)-[2-(2-chloropyridin-3-ylamino)-3,4-dioxo-1-cyclobuten-1-ylamino]-2,2-dimethylpropyl]-benzamide



C21 H19 Cl3 N4 O3; Mol wt: 481.7651

ACTION – Potassium (K_{ATP}) channel opener (EC_{50} = 2.6-5.5 μ M) able to suppress bladder contractions with an ED_{50} of 0.43 μ mol/kg in a pig model of bladder overactivity. In addition, it exhibited favorable pharmacokinetic properties with good oral bioavailability in dogs (80%, $t_{1/2}$ = 3.4 h). Potentially useful for the treatment of urinary incontinence.

SOURCE – Abbott.

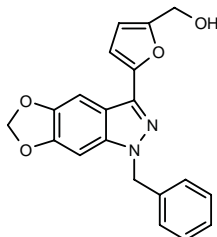
REFERENCES

1. Kort, M.E. et al. (Abbott Laboratories) *Aminal diones as potassium channel openers*. WO 0262761.
2. Kort, M.E. et al. *Aminal-containing ATP-sensitive potassium channel openers for the treatment of bladder overactivity*. 224th ACS Natl Meet (Aug 18-22, Boston) 2002, Abst MEDI 351.

ANTIPLATELET THERAPY

324849

1-[5-(1-Benzyl-1*H*-[1,3]dioxolo[4,5-*f*]indazol-3-yl)furan-2-yl]methanol



C20 H16 N2 O4; Mol wt: 348.3564

ACTION – A representative compound from a series of fused pyrazole derivatives with the ability to increase intracellular levels of cGMP, through either activation of soluble guanylate cyclase (sGC) or inhibition of phosphodiesterase (PDE). *In vitro*, it demonstrated sGC-activating and PDE-inhibitory activity. It also prevented platelet aggregation induced by thrombin, arachidonic acid, collagen and PAF. Potentially useful for the treatment of atherosclerosis, myocardial infarction, unstable angina, thrombosis and hypertension, as well as erectile dysfunction.

SOURCE – Yung Shin.

REFERENCES

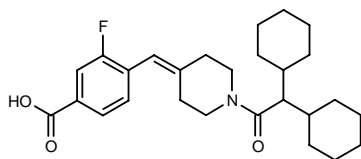
- Sheng-Chu, K. et al. (Yung Shin Pharm. Ind. Co. Ltd.) *Fused pyrazolyl cpds*. EP 1227099.

RENAL-UROLOGIC DRUGS

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SOURCE – Universität des Saarlandes, Saarbrücken (DE).

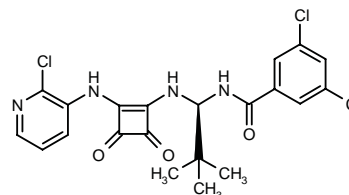
REFERENCES

- Picard, F. et al. *Synthesis and evaluation of 2'-substituted 4-(4'-carboxy- or 4'-carboxymethylbenzylidene)-N-acylpiperidines: Highly potent and in vivo active steroid 5 α -reductase type 2 inhibitors*. J Med Chem 2002, 45(16): 3406.
- Picard, F. et al. *Synthesis and evaluation of N-acyl-4-benzylidenepiperidines: Highly potent and in vivo active steroid-5 α -reductase type 2 inhibitors*. Drugs Fut 2002, 27(Suppl. A): Abst P425.

TREATMENT OF URINARY INCONTINENCE

323846

3,5-Dichloro-*N*-[1(*S*)-[2-(2-chloropyridin-3-ylamino)-3,4-dioxo-1-cyclobuten-1-ylamino]-2,2-dimethylpropyl]-benzamide



C21 H19 Cl3 N4 O3; Mol wt: 481.7651

ACTION – Potassium (K_{ATP}) channel opener (EC₅₀ = 2.6-5.5 μ M) able to suppress bladder contractions with an ED₅₀ of 0.43 μ mol/kg in a pig model of bladder overactivity. In addition, it exhibited favorable pharmacokinetic properties with good oral bioavailability in dogs (80%, t_{1/2} = 3.4 h). Potentially useful for the treatment of urinary incontinence.

SOURCE – Abbott.

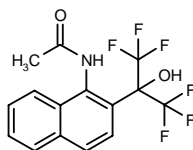
REFERENCES

- Kort, M.E. et al. (Abbott Laboratories) *Aminal diones as potassium channel openers*. WO 0262761.
- Kort, M.E. et al. *Aminal-containing ATP-sensitive potassium channel openers for the treatment of bladder overactivity*. 224th ACS Natl Meet (Aug 18-22, Boston) 2002, Abst MEDI 351.

A-151892

323880

N-[2-[2,2,2-Trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl]-naphthalen-1-yl]acetamide



C₁₅ H₁₁ F₆ N O₂; Mol wt: 351.2449

ACTION – Potent and selective potassium channel K_{ATP} opener ($K_i = 43$ nM) with little or no activity at HERG and Kv1.5 channels ($IC_{50} > 30$ μ M) and EC_{50} values of 18 and 20 nM for inhibition of calcium mobilization in human and guinea pig bladder cells, respectively. It also suppressed unstable contractions in rat and pig bladder instability models ($ED_{35} = 30$ nmol/kg and $ED_{30} = 6.7$ nmol/kg, respectively), with an estimated bladder selectivity ratio of 2.3. Compound exhibited an oral bioavailability of 22%. Potentially useful for the treatment of urinary incontinence.

SOURCES – Abbott; ICAGEN.

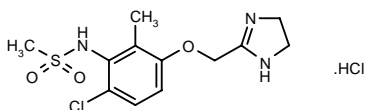
REFERENCES

1. Turner, S.C. et al. *The discovery of A-151892: A novel bladder selective K_{ATP} channel opener*. *Drugs Fut* 2002, 27(Suppl. A): Abstr C47.

RO-1151240

324230

N-[6-Chloro-3-(4,5-dihydro-1*H*-imidazol-2-ylmethoxy)-2-methylphenyl]methanesulfonamide hydrochloride



C₁₂ H₁₆ Cl N₃ O₃ S . HCl; Mol wt: 354.2563

ACTION – Selective α_{1A} -adrenoceptor partial agonist ($pK_i = 7.39, 5.80$ and 5.19 for binding affinity at α_{1A} , α_{1B} and α_{1D} -adrenoceptors, respectively) with a pEC_{50} of 6.79 in the inositol phosphate accumulation test. *In vivo*, compound dose-dependently increased the intraurethral pressure in anesthetized micropigs ($ED_{50} = 41.3$ μ g/kg i.v.) with minimal effects on blood pressure in conscious micropigs. Potentially useful for the treatment of urinary incontinence.

SOURCE – Roche.

REFERENCES

1. Cournoyer, R.L. et al. (Syntex [USA] LLC) *2-Imidazoline, 2-oxazoline, 2-thiazoline, and 4-imidazole derivs. of methylphenyl, methoxyphenyl, and aminophenyl alkylsulfonamides and ureas and their use*. EP 0887346, US 5952362.

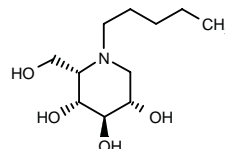
2. Odink, D.A. et al. (F. Hoffmann-La Roche AG) *Hydrolytically unstable compsns*. WO 0238133.

3. Blue, D. et al. *Pre-clinical pharmacology of RO1151240, a selective α_{1A} -adrenoceptor partial agonist being developed for the treatment of stress urinary incontinence*. 32nd Annu Meet Int Continence Soc (Aug 28-31, Heidelberg) 2002, Abstr 451.

TREATMENT OF RENAL DISEASES

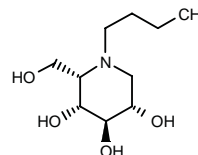
324311

2(*S*)-(Hydroxymethyl)-1-pentylpiperidine-3(*R*),4(*R*),5(*S*)-triol



C₁₁ H₂₃ N O₄; Mol wt: 233.3057

ACTION – An inhibitor of glucosylceramide synthase that exhibited less inhibitory activity against both glucosidases and galactosidases than previously known compounds and may therefore be associated with reduced side effects. Potential uses include polycystic kidney disease, diabetic renal hypertrophy, atherosclerosis, glycolipid storage diseases and obesity, among others. Another exemplified piperidine derivative is:



324314: C₁₀ H₂₁ N O₄

SOURCES – Oxford GlycoSciences; University of Oxford, Oxford (GB).

REFERENCES

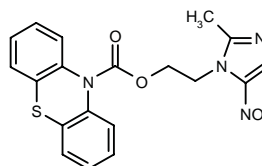
1. Butters, T.D. et al. (Oxford GlycoSciences Ltd.;University of Oxford) *Pharmaceutically active piperidine derivs*. WO 0255498.

GASTROINTESTINAL DRUGS

ANTIULCER DRUGS

324759

10*H*-Phenothiazine-10-carboxylic acid 2-(2-methyl-5-nitro-1*H*-imidazol-1-yl)ethyl ester

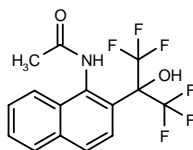


C₁₉ H₁₆ N₄ O₄ S; Mol wt: 396.4254

A-151892

323880

N-[2-[2,2,2-Trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl]-naphthalen-1-yl]acetamide



C₁₅ H₁₁ F₆ N O₂; Mol wt: 351.2449

ACTION – Potent and selective potassium channel K_{ATP} opener ($K_i = 43$ nM) with little or no activity at HERG and Kv1.5 channels ($IC_{50} > 30$ μ M) and EC_{50} values of 18 and 20 nM for inhibition of calcium mobilization in human and guinea pig bladder cells, respectively. It also suppressed unstable contractions in rat and pig bladder instability models ($ED_{35} = 30$ nmol/kg and $ED_{30} = 6.7$ nmol/kg, respectively), with an estimated bladder selectivity ratio of 2.3. Compound exhibited an oral bioavailability of 22%. Potentially useful for the treatment of urinary incontinence.

SOURCES – Abbott; ICAGEN.

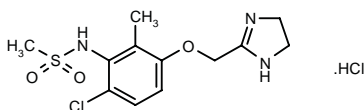
REFERENCES

1. Turner, S.C. et al. *The discovery of A-151892: A novel bladder selective K_{ATP} channel opener*. *Drugs Fut* 2002, 27(Suppl. A): Abstr C47.

RO-1151240

324230

N-[6-Chloro-3-(4,5-dihydro-1*H*-imidazol-2-ylmethoxy)-2-methylphenyl]methanesulfonamide hydrochloride



C₁₂ H₁₆ Cl N₃ O₃ S . HCl; Mol wt: 354.2563

ACTION – Selective α_{1A} -adrenoceptor partial agonist ($pK_i = 7.39, 5.80$ and 5.19 for binding affinity at α_{1A} , α_{1B} and α_{1D} -adrenoceptors, respectively) with a pEC_{50} of 6.79 in the inositol phosphate accumulation test. *In vivo*, compound dose-dependently increased the intraurethral pressure in anesthetized micropigs ($ED_{50} = 41.3$ μ g/kg i.v.) with minimal effects on blood pressure in conscious micropigs. Potentially useful for the treatment of urinary incontinence.

SOURCE – Roche.

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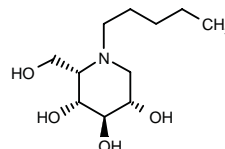
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3. Blue, D. et al. *Pre-clinical pharmacology of RO1151240, a selective α_{1A} -adrenoceptor partial agonist being developed for the treatment of stress urinary incontinence*. 32nd Annu Meet Int Continence Soc (Aug 28-31, Heidelberg) 2002, Abstr 451.

TREATMENT OF RENAL DISEASES

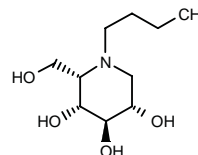
324311

2(*S*)-(Hydroxymethyl)-1-pentylpiperidine-3(*R*),4(*R*),5(*S*)-triol



C₁₁ H₂₃ N O₄; Mol wt: 233.3057

ACTION – An inhibitor of glucosylceramide synthase that exhibited less inhibitory activity against both glucosidases and galactosidases than previously known compounds and may therefore be associated with reduced side effects. Potential uses include polycystic kidney disease, diabetic renal hypertrophy, atherosclerosis, glycolipid storage diseases and obesity, among others. Another exemplified piperidine derivative is:



324314: C₁₀ H₂₁ N O₄

SOURCES – Oxford GlycoSciences; University of Oxford, Oxford (GB).

REFERENCES

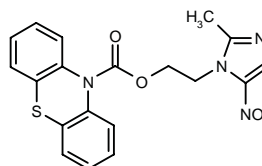
1. Butters, T.D. et al. (Oxford GlycoSciences Ltd.;University of Oxford) *Pharmaceutically active piperidine derivs*. WO 0255498.

GASTROINTESTINAL DRUGS

ANTIULCER DRUGS

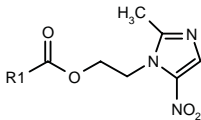
324759

10*H*-Phenothiazine-10-carboxylic acid 2-(2-methyl-5-nitro-1*H*-imidazol-1-yl)ethyl ester



C₁₉ H₁₆ N₄ O₄ S; Mol wt: 396.4254

ACTION – Anti-*Helicobacter pylori* agent proven active *in vitro* against *H. pylori* ATCC 43579 and OSU strains, with an MBC (lowest concentration that killed 100% of the *H. pylori* working solution) of 10.3 µg/ml. Other exemplified nitroimidazole ester analogues are:



Compound	R1	Formula
324760	3-Pyr	C ₁₂ H ₁₂ N ₄ O ₄
324763	2-Ph-4-quinolinyl	C ₂₂ H ₁₈ N ₄ O ₄

SOURCE – California Pacific Medical Center Institute, San Francisco, CA (US).

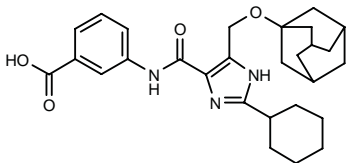
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1. Yang, L.-X. et al. (California Pacific Medical Center Institute) *Nitroimidazole ester analogues and therapeutic applications*. US 6423707.

JB-99157*

313133

3-[5-(Adamant-1-yloxymethyl)-2-cyclohexyl-1H-imidazol-4-ylcarboxamido]benzoic acid



C28 H35 N3 O4; Mol wt: 477.6015

ACTION – Potent and selective gastrin/CCK₂ receptor antagonist (pK_B = 8.6) with good *in vivo* potency in a model of pentagastrin-stimulated acid secretion following enteral administration (ID₅₀ = 3 mg/kg). Potentially useful as an antiulcer agent.

SOURCES – James Black Foundation; Janssen.

REFERENCES

1. Kalindjian, S.B. et al. (James Black Foundation Ltd.) *Gastrin and cholecystokinin receptor ligands*. WO 0027823.

2. Kalindjian, S.B. et al. (Janssen Pharmaceutica NV; James Black Foundation Ltd.) *Pharmaceutical compsns. comprising proton pump inhibitors and gastrin/cholecystokinin receptor ligands*. WO 0185167.

3. McDonald, I.M. et al. *JB99157, a selective gastrin/CCK2 receptor antagonist with high in vitro and in vivo potency*. *Drugs Fut* 2002, 27(Suppl. A): Abst P373.

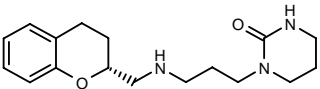
*Identified compound 313133 Drug Data Rep 2002, 024(02): 0137.

AGENTS FOR
NONULCER DYSPEPSIA

R-137696*

277810

(-)-1-[3-[3,4-Dihydro-2H-1-benzopyran-2(R)-ylmethyl-amino]propyl]perhydropyrimidin-2-one



C17 H25 N3 O2; Mol wt: 303.4035

ACTION – 5-HT_{1A} agonist (pIC₅₀ = 7.9), a benzopyran derivative with fundus-relaxing properties, potentially useful for the treatment of functional dyspepsia. Currently in clinical evaluation.

SOURCE – Janssen.

REFERENCES

1. Wigerinck, P.T.B.P. et al. (Janssen Pharmaceutica NV) *(Benzodioxan, benzofuran or benzopyran) derivs. having fundic relaxation properties*. EP 1036073, JP 2001525407, US 6133277, WO 9929687.

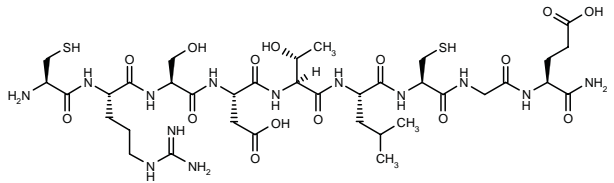
2. De Bruyn, M. et al. *Discovery of R137696, a fundus relaxing compound for the treatment of functional dyspepsia*. *Drugs Fut* 2002, 27(Suppl. A): Abst P202.

*Identified compound 277810 Drug Data Rep 1999, 021(08): 0705.

AGENTS FOR
INFLAMMATORY BOWEL DISEASE

322888

L-Cysteiny-L-arginyl-L-seryl-L-aspartyl-L-threonyl-L-leucyl-L-cysteiny-L-glycyl-L-glutamide



C36 H63 N13 O15 S2; Mol wt: 982.1017

ACTION – Potent and selective integrin α₄β₇ antagonist (IC₅₀ = 0.03 µM) with antiinflammatory activity in IL-10 knockout mice with spontaneous colitis. In this model, compound inhibited the mucosal addressin cell adhesion molecule (MAdCAM)-dependent lymphocyte accumulation in the large intestine when given at a dose of 50 mg/kg i.v. prior to injection with ⁵¹Cr-labeled mesenteric lymph node cells. No inhibition of lymphocyte migration to peripheral inguinal lymph nodes where MAdCAM is not overexpressed was seen. Potentially useful for the treatment of inflammatory bowel disease.

SOURCE – Genentech.

REFERENCES

1. Dubree, N.J.P. et al. *Selective $\alpha 4\beta 7$ integrin antagonists and their potential as antiinflammatory agents*. J Med Chem 2002, 45(16): 3451.

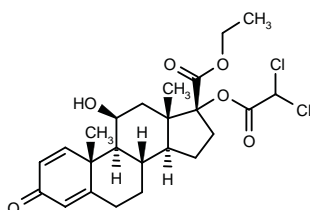
ETIPREDNOL DICLOACETATE

USAN

307322

(11 β ,17 α)-17-(2,2-Dichloroacetoxy)-11-hydroxy-3-oxo-androsta-1,4-diene-17-carboxylic acid ethyl ester

BNP-166



C24 H30 Cl2 O6; Mol wt: 485.4010

ACTION – Soft corticosteroid with affinity for glucocorticoid receptors and *in vivo* antiinflammatory activity comparable to budesonide but lower systemic side effects after 28-day oral dosing in rats and dogs; the no-adverse-effect level (NOAEL) was 2 mg/kg p.o. in rats and dogs, 40 times higher than that of budesonide. Potentially useful for the treatment of inflammatory bowel disease.

SOURCE – Ivax.

REFERENCES

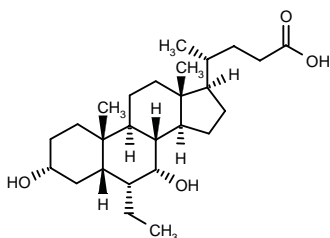
1. Bodor, N.S. (Soft Drugs, Inc.) *Androstene derivs*. WO 9742214.
2. Miklos, A. et al. *28-Day oral toxicity study with soft corticosteroid BNP-166 in rats and dogs, followed by a 14-day recovery period*. Pharmazie 2002, 57(2): 142.
3. Zubovics, Z. et al. *Impurity profile of the soft drug candidate BNP-166*. Drugs Fut 2002, 27(Suppl. A): Abst P552.
4. Ivax announces encouraging phase I results of BNP-166 as treatment of Crohn's disease. DailyDrugNews.com (Daily Essentials) 2001, Aug 27.
5. Phase Ib study of BNP-166 successfully completed. DailyDrugNews.com (Daily Essentials) 2002, March 27.

TREATMENT OF LIVER AND BILIARY TRACT DISORDERS

6-ECDCA

323123

(3 α ,5 β ,6 α ,7 α)-6-Ethyl-3,7-dihydroxycholan-24-oic acid



C26 H44 O4; Mol wt: 420.6296

ACTION – Potent and selective steroidal farnesoid X receptor (FXR) agonist (EC_{50} = 99 nM) with potent full agonist activity in a reporter gene assay using human FXR receptors expressed in HuH7 cells (EC_{50} = 85 nM), but no activity at other receptors at 1 μ M. In rats, compound at a dose of 3 μ mol/kg/min i.v. fully reversed cholestasis and liver injury induced by lithocholic acid. No intrinsic cholestatic activity or acute liver toxicity was seen. Potentially useful for the treatment of cholestatic liver disease.

SOURCE – GlaxoSmithKline.

REFERENCES

1. Pellicciari, R. et al. *6 α -Ethyl-chenodeoxycholic acid (6-ECDCA), a potent and selective FXR agonist endowed with anticholestatic activity*. J Med Chem 2002, 45(17): 3569.

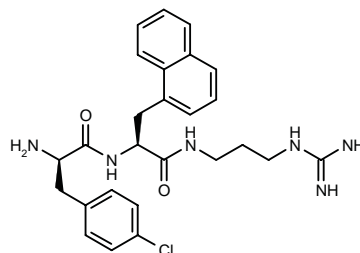
TREATMENT OF PANCREATIC DISORDERS

FE-999024

323877

4-Chloro-D-phenylalanyl-3-(1-naphthyl)-L-alanine 3-guadinopropylamide

CH-2856



C26 H31 Cl N6 O2; Mol wt: 495.0239

ACTION – Human tissue kallikrein 1 (hK1) inhibitor (K_i = 0.002 μ M), stable to proteolytic cleavage and selective over other trypsin-like serine proteases (K_i = 1.0, 35.0, 1.0 and 10.8 μ M for inhibition of plasma kallikrein, thrombin, trypsin and plasmin, respectively). In a rat model of cerulein-induced acute pancreatitis, compound dose-dependently (7-60 μ mol/kg i.p.) reduced edema and plasma protein extravasation. Other experiments showed that compound dose-dependently (1.25-10 mg/kg i.p.) reduced the allergen-induced eosinophilia in sensitized guinea pigs; the effect at the higher dose compared favorably with betamethasone (4 mg/kg i.p.). Potentially useful for the treatment of acute pancreatitis, as well as asthma.

SOURCE – Ferring.

REFERENCES

1. Szelke, M. et al. (Ferring AB) *Kininogen inhibitors*. EP 0736036, JP 1997502434, WO 9507291.
2. Evans, D.M. et al. *Potent low molecular weight inhibitors of human tissue kallikrein hK1 and their activity in a model of acute pancreatitis*. Drugs Fut 2002, 27(Suppl. A): Abst P233.

3. Evans, D.M. et al. *Synthetic inhibitors of human tissue kallikrein*. Immunopharmacology 1996, 32(1-3): 117.

4. Griesbacher, T. et al. *Inhibition of kinin action and kinin generation compared to dexamethasone pretreatment with respect to vascular effects and pancreatic enzymes in experimental acute pancreatitis*. Immunopharmacology 1999, 43(2-3): 219.

5. Griesbacher, T. et al. *Mechanisms of kinin release during acute cerulein-induced pancreatitis*. Dig Dis Week (May 20-23, Atlanta) 2001, Abst 2734.

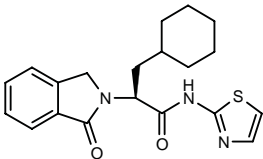
6. Wolf, W.C. et al. *A synthetic tissue kallikrein inhibitor suppresses cancer cell invasiveness*. Am J Pathol 2001, 159(5): 1797.

ENDOCRINE DRUGS

ANTIDIABETIC DRUGS

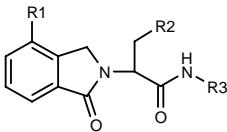
323220

3-Cyclohexyl-2(*S*)-(1-oxo-2,3-dihydro-1*H*-isoindol-2-yl)-*N*-(2-thiazolyl)propionamide



C20 H23 N3 O2 S; Mol wt: 369.4867

ACTION – Glucokinase activator with potential in the treatment of type 2 diabetes. The compound demonstrated glucokinase-activating effects *in vitro* and *in vivo* following oral administration to mice at a dose of 50 mg/kg. Other exemplified isoindolin-1-one derivatives are:



Compound	R1	R2	R3	Isomer	Formula
323221	H	cyclopentyl	5-Cl-2-thiazolyl		C ₁₉ H ₂₀ ClN ₃ O ₂ S
323222	H	cyclohexyl	5-Br-2-Pyr	S	C ₂₂ H ₂₄ BrN ₃ O ₂
323223	F	cyclohexyl	2-thiazolyl	S	C ₂₀ H ₂₂ FN ₃ O ₂ S
323224	F	cyclohexyl	2-pyrazinyl	S	C ₂₁ H ₂₃ FN ₄ O ₂
323225	H	cyclohexyl	2-Pyr	S	C ₂₂ H ₂₅ N ₃ O ₂
323226	H	cyclohexyl	4-pyrimidinyl	S	C ₂₁ H ₂₄ N ₄ O ₂
323227	H	cyclohexyl	2-pyrazinyl	S	C ₂₁ H ₂₄ N ₄ O ₂
323228	H	cyclohexyl	5-Me-2-Pyr	S	C ₂₃ H ₂₇ N ₃ O ₂
323229	H	cyclohexyl	5-Cl-2-Pyr	S	C ₂₂ H ₂₄ ClN ₃ O ₂

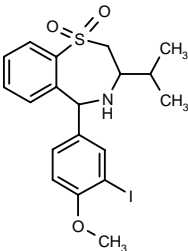
SOURCE – Roche.

REFERENCES

1. Guertin, K.R. (F. Hoffmann-La Roche AG) *Isoindolin-1-one glucokinase activators*. WO 0248106.

324280

5-(3-Iodo-4-methoxyphenyl)-3-isopropyl-2,3,4,5-tetrahydro-1,4-benzothiazepine *S,S*-dioxide



C19 H22 I N O3 S; Mol wt: 471.3528

ACTION – A representative compound from a series of benzothiazepine derivatives with the ability to increase blood glucagon-like peptide-1 (GLP-1) levels, potentially useful for the treatment of diabetes and complications thereof.

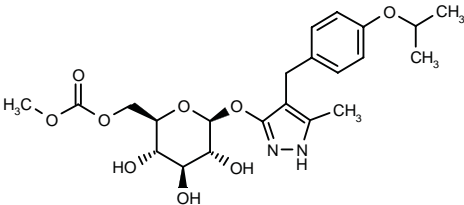
SOURCE – Banyu.

REFERENCES

1. Nagase, T. et al. (Banyu Pharmaceutical Co., Ltd.) *Benzothiazepine derivs*. WO 0253548.

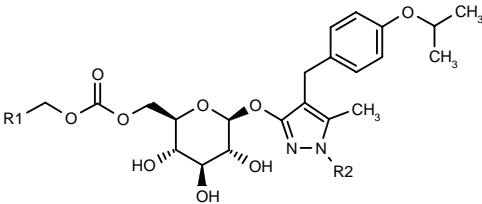
324320

1-*O*-[4-(4-Isopropoxybenzyl)-5-methyl-1*H*-pyrazol-3-yl]-6-*O*-(methoxycarbonyl)-β-*D*-glucopyranoside



C22 H30 N2 O9; Mol wt: 466.4840

ACTION – An inhibitor of the sodium-dependent glucose transporter SGLT-2 with improved oral bioavailability, giving an IC₅₀ of 679 nM against SGLT-2; no deaths were observed in acute toxicity testing in mice administered up to 2000 mg/kg p.o. Potentially useful for the treatment of diabetes, diabetic complications and obesity, among other disorders associated with hyperglycemia. Other exemplified glucopyranosylpyrazole derivatives are:



Compound	R1	R2	Formula
324322	Me	i-Pr	C ₂₆ H ₃₈ N ₂ O ₉
324323	H	i-Pr	C ₂₅ H ₃₆ N ₂ O ₉
324324	i-Pr	i-Pr	C ₂₈ H ₄₂ N ₂ O ₉
324325	Me	H	C ₂₃ H ₃₂ N ₂ O ₉

3. Evans, D.M. et al. *Synthetic inhibitors of human tissue kallikrein*. Immunopharmacology 1996, 32(1-3): 117.

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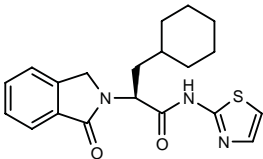
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ENDOCRINE DRUGS

ANTIDIABETIC DRUGS

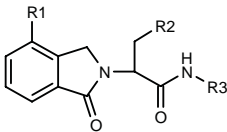
323220

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323224	F	cyclohexyl	2-pyrazinyl	S	C ₂₁ H ₂₃ FN ₄ O ₂
323225	H	cyclohexyl	2-Pyr	S	C ₂₂ H ₂₅ N ₃ O ₂
323226	H	cyclohexyl	4-pyrimidinyl	S	C ₂₁ H ₂₄ N ₄ O ₂
323227	H	cyclohexyl	2-pyrazinyl	S	C ₂₁ H ₂₄ N ₄ O ₂
323228	H	cyclohexyl	5-Me-2-Pyr	S	C ₂₃ H ₂₇ N ₃ O ₂
323229	H	cyclohexyl	5-Cl-2-Pyr	S	C ₂₂ H ₂₄ ClN ₃ O ₂

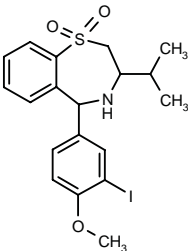
SOURCE – Roche.

REFERENCES

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324280

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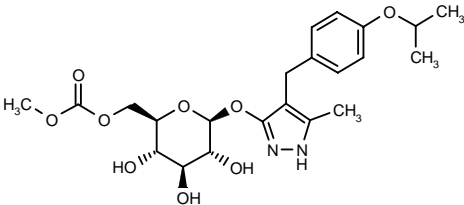
SOURCE – Banyu.

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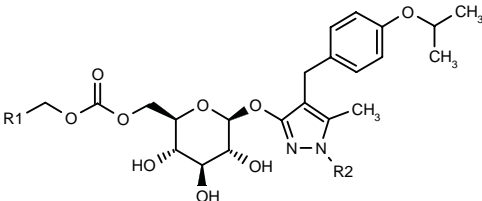
324320

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324323	H	i-Pr	C ₂₅ H ₃₆ N ₂ O ₉
324324	i-Pr	i-Pr	C ₂₈ H ₄₂ N ₂ O ₉
324325	Me	H	C ₂₃ H ₃₂ N ₂ O ₉

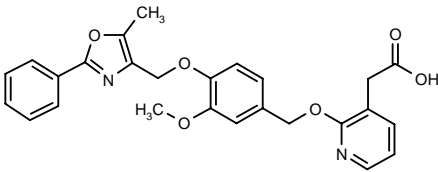
SOURCE – Kissei.

REFERENCES

1. Fujikura, H. et al. (Kissei Pharmaceutical Co., Ltd.) *Glucopyranosyloxypyrazole derivs. and use thereof in medicines.* WO 0253573.

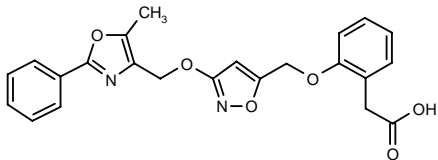
324334

2-[2-[3-Methoxy-4-(5-methyl-2-phenyloxazol-4-yl-methoxy)benzyloxy]pyridin-3-yl]acetic acid

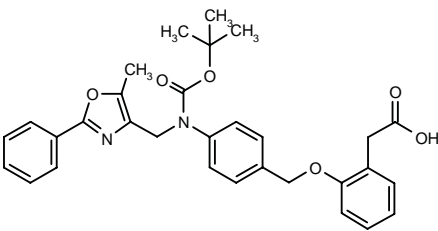


C26 H24 N2 O6; Mol wt: 460.4836

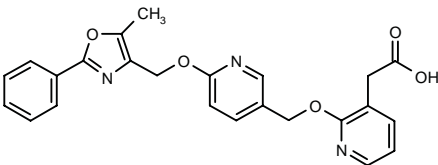
ACTION – Agent with blood glucose- and lipid-lowering activity, potentially useful for the treatment of diabetes, hyperlipidemia and impaired glucose tolerance. Compound decreased blood glucose and triglyceride levels by 50 and 67%, respectively, when administered in the diet at 0.005%. It also lowered total cholesterol levels in animal models and it exhibited high affinity for heterodimer receptors formed from retinoid X receptor RXRα and peroxisome proliferator-activated receptor PPARγ. Other exemplified alkanolic acid derivatives are:



324335: C23 H20 N2 O6



324336: C31 H32 N2 O6



324337: C24 H21 N3 O5

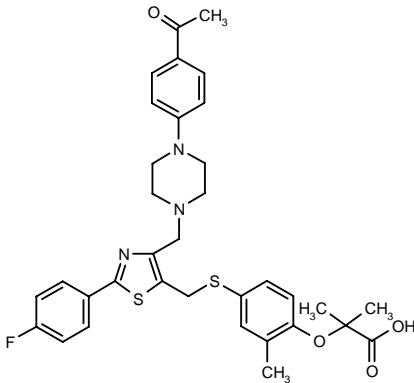
SOURCE – Takeda.

REFERENCES

1. Momose, Y. et al. (Takeda Chemical Industries, Ltd.) *Alkanolic acid derivs., process for their production and use thereof.* WO 0253547.

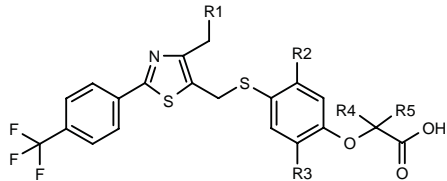
324870

2-[4-[4-[4-(4-Acetylphenyl)piperazin-1-ylmethyl]-2-(4-fluorophenyl)thiazol-5-ylmethylsulfanyl]-2-methylphenoxy]-2-methylpropionic acid



C34 H36 F N3 O4 S2; Mol wt: 633.8054

ACTION – Peroxisome proliferator-activated receptor (PPAR) agonist with potential in the treatment of dyslipidemia, syndrome X, heart failure, hypercholesterolemia, cardiovascular disease, type 1 and type 2 diabetes, insulin resistance, hyperlipidemia, obesity and anorexia. Other specifically claimed compounds include the following:



Compound	R1	R2	R3	R4	R5	Formula
324873	Ph	Me	Me	H	H	C ₂₈ H ₂₄ F ₃ N ₃ O ₃ S ₂
324874	4-(PhOCO)-1-Piz	H	Me	Me	Me	C ₃₄ H ₃₄ F ₃ N ₃ O ₅ S ₂
324875	4-(4-MeO-Ph)-1-Piz	H	i-Pr	H	H	C ₃₄ H ₃₆ F ₃ N ₃ O ₄ S ₂
324876	4-(4-Ac-Ph)-1-Piz	H	Pr	H	H	C ₃₅ H ₃₆ F ₃ N ₃ O ₄ S ₂
324877	4-(4-Cl-Ph)-1-Piz	H	Me	H	Me	C ₃₂ H ₃₁ ClF ₃ N ₃ O ₃ S ₂
324878	4-(2-pyrazinyl)-1-Piz	H	Me	H	H	C ₂₈ H ₂₈ F ₃ N ₅ O ₃ S ₂
324879	4-(4-MeO-Ph)-1-Piz	H	Me	H	Me	C ₃₃ H ₃₄ F ₃ N ₃ O ₄ S ₂
324880	4-(4-i-PrO-Ph)-1-Piz	H	Me	H	Me	C ₃₅ H ₃₈ F ₃ N ₃ O ₄ S ₂

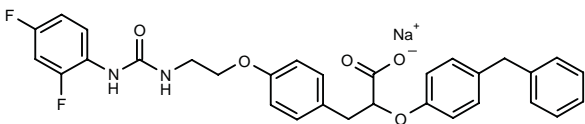
SOURCE – GlaxoSmithKline.

REFERENCES

1. Banker, P. et al. (GlaxoSmithKline plc) *Thiazole and oxazole derivs. as activators of human peroxisome proliferator activated receptors.* WO 0259098.

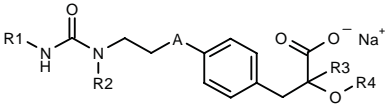
325119

2-(4-Benzylphenoxy)-3-[4-[2-[3-(2,4-difluorophenyl)-ureido]ethoxy]phenyl]propionic acid sodium salt

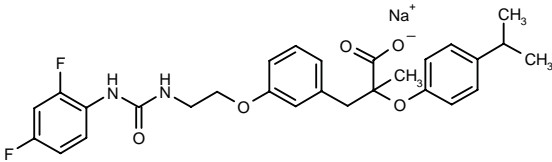


C31 H27 F2 N2 Na O5; Mol wt: 568.5493

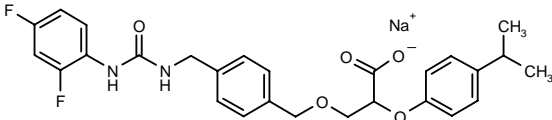
ACTION – Blood glucose- and lipid-lowering agent, potentially useful for the treatment of diabetes, hyperlipidemia and impaired glucose tolerance. In the KKA^y mouse model of obesity and type 2 diabetes, orally administered compound (0.008% in the diet) resulted in 69 and 92% reductions, respectively, in blood glucose and triglyceride levels. Other exemplified compounds are:



Compound	R1	R2	R3	R4	A	Formula
325120	2,4-(F)2-Ph	C7H15	Me	4-i-Pr-Ph	-O-	C ₃₅ H ₄₃ F ₂ N ₂ NaO ₅
325121	cyclohexyl	C7H15	Me	4-i-Pr-Ph	-O-	C ₃₅ H ₅₁ N ₂ NaO ₅
325123	Ph	C7H15	Me	4-i-Pr-Ph	-O-	C ₃₅ H ₄₅ N ₂ NaO ₅
325124	2,4-(F)2-Ph	C10H21	Me	4-i-Pr-Ph	-O-	C ₃₈ H ₄₉ F ₂ N ₂ NaO ₅
325125	2,4-(F)2-Ph	H	Me	4-i-Pr-Ph	-O-	C ₂₈ H ₂₉ F ₂ N ₂ NaO ₅
325126	2,4-(F)2-Ph	C7H15	H	4-i-Pr-Ph	-O-	C ₃₄ H ₄₁ F ₂ N ₂ NaO ₅
325128	2,4-(F)2-Ph	C7H15	Me	4-i-Pr-Ph	bond	C ₃₅ H ₄₃ F ₂ N ₂ NaO ₄
325129	2,4-(F)2-Ph	C7H15	Me	4-i-Pr-Ph	-CH2-	C ₃₆ H ₄₅ F ₂ N ₂ NaO ₄
325130	2,4-(F)2-Ph	H	Me	Ph	-O-	C ₂₅ H ₂₃ F ₂ N ₂ NaO ₅
325131	2,4-(F)2-Ph	H	H	4-N(Me)2-Ph	-O-	C ₂₆ H ₂₆ F ₂ N ₃ NaO ₅
325132	2,4-(F)2-Ph	H	H	4-F-PhCH2	-O-	C ₂₅ H ₂₂ F ₃ N ₂ NaO ₅



325127: C28 H29 F2 N2 Na O5



325133: C33 H31 F2 N2 Na O5

SOURCE – Toa Eiyo.

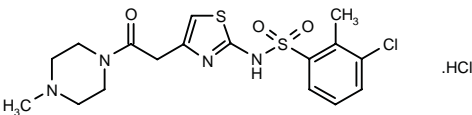
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1. Sato, H. et al. (Toa Eiyo Ltd.) *Urea carboxylic acid derivs.* JP 2002201171.

BVT-2733

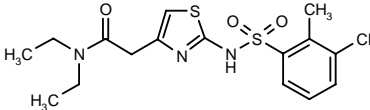
321182

3-Chloro-2-methyl-N-[4-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]thiazol-2-yl]benzenesulfonamide hydrochloride



C17 H21 Cl N4 O3 S2 . HCl; Mol wt: 465.4238

ACTION – Potent and selective inhibitor of 11 β -hydroxy-steroid dehydrogenase type 1 (11 β -HSD1; K_i = 3.34 and 0.096 μ M against human and mouse enzyme, respectively) with high selectivity over 11 β -HSD2 (K_i > 10 μ M). In diabetic KKA^y mice, compound at doses of 25-100 mg/kg p.o. significantly lowered blood glucose levels in a dose-dependent manner, with a maximum effect of 53% after 11 days of treatment with the highest dose. In addition, 1-week treatment at a dose of 167 mg/kg/day using osmotic minipumps produced significant reductions in hepatic mRNA levels of two enzymes involved in hepatic glucose production: phosphoenolpyruvate car-boxykinase (75%) and glucose-6-phosphatase (55%). Potentially useful for the treatment of type 2 diabetes. Another related compound is:



BVT-14225 [324448]^{1,4,5}: C16 H20 Cl N3 O3 S2

SOURCE – Biovitrum.

REFERENCES

1. Barf, T. et al. (Biovitrum AB) *Inhibitors of 11- β -hydroxy steroid dehydrogenase type 1.* WO 0190090.

2. Alberts, P. et al. *The selective 11 β -hydroxysteroid dehydrogenase type 1 (11 β -HSD1) inhibitor BVT.2733 administered orally lowers blood glucose levels in hyperglycemic KKA^y, ob/ob, and db/db mice.* 84th Annu Meet Endocr Soc (June 19-22, San Francisco) 2002, Abst P3-392.

3. Alberts, P. et al. *The selective 11 β -hydroxysteroid dehydrogenase type 1 (11 β -HSD1) inhibitor BVT.2733 lowers blood glucose levels in hyperglycemic KKA^y mice.* Diabetes 2002, 51(Suppl. 2): Abst 172-OR.

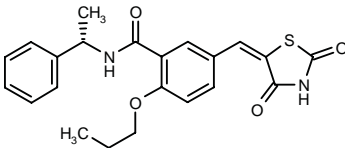
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GW-500580X

324074

5-[(E)-(2,4-Dioxothiazolidin-5-ylidenemethyl)-N-[1(S)-phenylethyl]-2-propoxybenzamide



C22 H22 N2 O4 S; Mol wt: 410.4918

ACTION – β -Cell potassium K_{ATP} channel agonist (pIC₅₀ = 7.23) shown to normalize glucose and insulin levels in obese ob/ob mice. Its ability to reduce insulin levels upon acute dosing indicated that it acts via a non-PPAR (peroxisome proliferator-activated receptor) mechanism. Potentially useful for the treatment of type 2 diabetes.

SOURCE – GlaxoSmithKline.

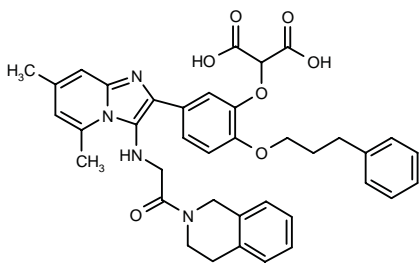
REFERENCES

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MC-52201

324290

2-[5-[3-[2-(1,2,3,4-Tetrahydroisoquinolin-2-yl)-2-oxo-ethylamino]-5,7-dimethylimidazo[1,2-*a*]pyridin-2-yl]-2-(3-phenylpropoxy)phenoxy]malonic acid



C38 H38 N4 O7; Mol wt: 662.7392

ACTION – Protein-tyrosine-phosphatase PTP1B inhibitor (IC_{50} = 0.7 μ M) with high selectivity over other phosphatases including TCTTP, LAR and CD45 (IC_{50} = 44.2, 118 and 57.9 μ M, respectively). Potentially useful for the treatment of type 2 diabetes, insulin resistance and obesity.

SOURCE – Morphochem.

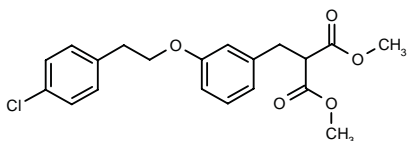
REFERENCES

1. Behnke, D. et al. *Imidazo[1,2-*a*]pyridines via a three component reaction as inhibitors of protein tyrosine phosphatase 1B*. Drugs Fut 2002, 27(Suppl. A): Abst P132.

ST-1863

324396

2-[3-[2-(4-Chlorophenyl)ethoxy]benzyl]malonic acid dimethyl diester



C20 H21 Cl O5; Mol wt: 376.8339

ACTION – Insulin sensitizer able to increase glucose utilization in 3T3-L1 cells (40% at 1 μ M) and to significantly reduce serum glucose (32%) and triglyceride levels (47%) in diabetic *db/db* mice at a dose of 25 mg/kg b.i.d. p.o. Compared to rosiglitazone, compound exhibited similar *in vitro* and *in vivo* activity, but it was associated with less weight gain and significantly less hepatotoxicity. Moreover, only compound significantly increased serum HDL cholesterol levels (37%) in these animals. Potentially useful for the treatment of type 2 diabetes.

SOURCE – Sigma-Tau.

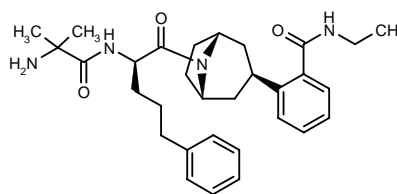
REFERENCES

1. Arduini, A. et al. *New phenylalkylcarboxylate derivatives as hypoglycemic and hypolipidemic agents*. Drugs Fut 2002, 27(Suppl. A): Abst P259.

TREATMENT OF GROWTH HORMONE SECRETION DISORDERS

324007

2-[8-[2(*R*)-(2-Amino-2-methylpropionylamino)-5-phenylpentanoyl]-8-azabicyclo[3.2.1]oct-3-*exo*-yl]-*N*-ethylbenzamide



C31 H42 N4 O3; Mol wt: 518.6978

ACTION – Growth hormone (GH) secretagogue with an EC_{50} value of 1.3 nM in a rat pituitary cell assay and good oral bioavailability in dogs. An oral dose of 0.25 mg/kg produced strong and long-lasting GH release in dogs; serum GH levels rose from a basal level of 1.7 ng/ml to 55 ng/ml at 30 min and returned to baseline after 3 h. Potentially useful for the treatment of GH deficiency.

SOURCE – Merck & Co.

REFERENCES

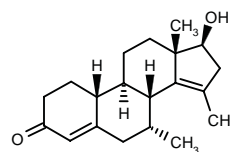
1. Lu, Z. et al. (Merck & Co., Inc.) *Bridged piperidines promote release of growth hormone*. US 5731317.

2. Lu, Z. et al. *Substituted bridged phenyl piperidines: Orally active growth hormone secretagogues*. 224th ACS Natl Meet (Aug 18-22, Boston) 2002, Abst MEDI 371.

TREATMENT OF MALE SEXUAL DYSFUNCTION

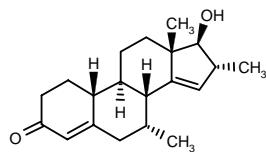
322942

(7 α ,17 β)-17-Hydroxy-7,15-dimethylestra-4,14-dien-3-one



C20 H28 O2; Mol wt: 300.4392

ACTION – Synthetic androgen for use as a dual androgenic/progestagenic agent in hormone replacement therapy. In *in vitro* testing, compound demonstrated a mixed profile with a 1:1 ratio between the androgenic and the progestagenic potency. Another specifically claimed compound is:



322943: C20 H28 O2

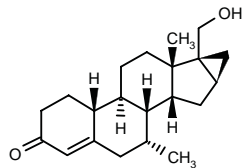
SOURCE – Akzo Nobel.

REFERENCES

1. Van der Louw, J. et al. (Akzo Nobel N.V.) *14(15)-Unsaturated 15- and/or 16-substd. androgens with mixed androgen-progestational profile.* WO 0248169.

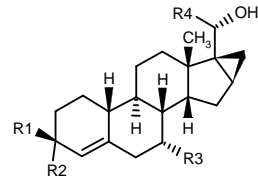
322945

(7 α ,14 β ,16 β ,17 β)-17-(Hydroxymethyl)-7-methyl-16,17-methyleneestr-4-en-3-one

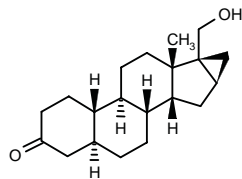


C21 H30 O2; Mol wt: 314.4660

ACTION – Potent synthetic androgen for use in hormone replacement therapy. Other exemplified methylene steroids are:



Compound	R1	R2	R3	R4	Isomer	Formula
322947	-O-		Me	Me		C ₂₂ H ₃₂ O ₂
322948	-O-		Me	Et		C ₂₃ H ₃₄ O ₂
322949	-O-		Me	ethynyl		C ₂₃ H ₃₀ O ₂
322952	OH	H	Me	H		C ₂₁ H ₃₂ O ₂
322954	-N(OH)-		Me	H	E	C ₂₁ H ₃₁ NO ₂
322955	-N(OH)-		Me	H	Z	C ₂₁ H ₃₁ NO ₂
322957	-O-		H	H		C ₂₀ H ₂₈ O ₂



322959: C20 H30 O2

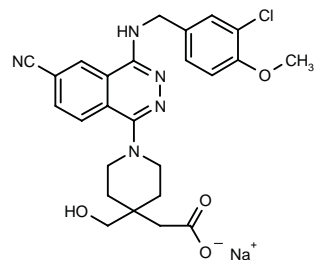
SOURCE – Akzo Nobel.

REFERENCES

1. Van der Louw, J. et al. (Akzo Nobel N.V.) *Methylene steroids as novel androgens.* WO 0248171.

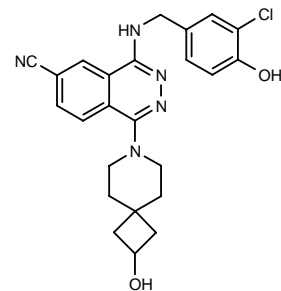
324505

2-[1-[4-(3-Chloro-4-methoxybenzylamino)-6-cyanophthalazin-1-yl]-4-(hydroxymethyl)piperidin-4-yl]acetic acid sodium salt



C25 H25 Cl N5 Na O4; Mol wt: 517.9465

ACTION – Phosphodiesterase type 5 (PDE5) inhibitor that displayed an IC₅₀ of 0.40 nM against cGMP-specific PDE from human platelets. Potentially useful for the treatment of erectile dysfunction, female sexual dysfunction, dysmenorrhea, hypertension, pulmonary hypertension, angina pectoris and other cardiopathies, diabetes and nephropathies. Another exemplified phthalazine derivative is:



324506: C24 H24 Cl N5 O2

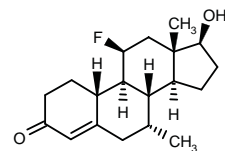
SOURCE – Eisai.

REFERENCES

1. Watanabe, N. et al. (Eisai Co., Ltd.) *Novel phthalazine cpds. and therapeutic agents for erectile dysfunction.* JP 2002179674.

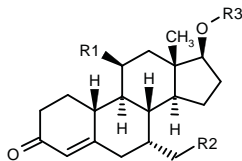
324959

11 β -Fluoro-17 β -hydroxy-7 α -methylestr-4-en-3-one

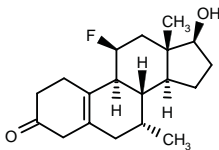


C19 H27 F O2; Mol wt: 306.4183

ACTION – Androgenic steroid shown to promote androgen-mediated increases in the weight of the prostate, seminal vesicles and levator ani following administration to juvenile male castrated rats. Other specifically claimed 11 β -halogen-substituted steroid derivatives are:



Compound	R1	R2	R3	Formula
324960	Cl	H	H	C ₁₉ H ₂₇ ClO ₂
324961	Br	H	H	C ₁₉ H ₂₇ BrO ₂
324962	I	H	H	C ₁₉ H ₂₇ IO ₂
324963	F	Me	H	C ₂₀ H ₂₉ FO ₂
324964	F	F	H	C ₁₉ H ₂₆ F ₂ O ₂
324965	F	H	COC6H13	C ₂₆ H ₃₉ FO ₃
324966	F	H	COC10H21	C ₃₀ H ₄₇ FO ₃



324968: C19 H27 F O2

SOURCE – Schering AG.

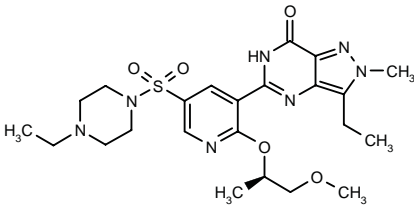
REFERENCES

1. Bohlmann, R. et al. (Schering AG) *Androgenic 7-substd. 11-halogen steroid*. DE 10104327, WO 0259139.

UK-371800

323631

3-Ethyl-5-[5-(4-ethylpiperazin-1-ylsulfonyl)-2-[2-methoxy-1(*R*)-methylethoxy]pyridin-3-yl]-2-methyl-6,7-dihydro-2*H*-pyrazolo[4,3-*d*]pyrimidin-7-one



C24 H34 N6 O5 S; Mol wt: 518.6356

ACTION – Phosphodiesterase type 5 (PDE5) inhibitor with comparable potency to sildenafil (IC₅₀ = 4.2 and 3.5 nM, respectively) but much more selective over PDE6 (IC₅₀ = 417 and 38 nM, respectively). Potentially useful for the treatment of erectile dysfunction.

SOURCE – Pfizer.

REFERENCES

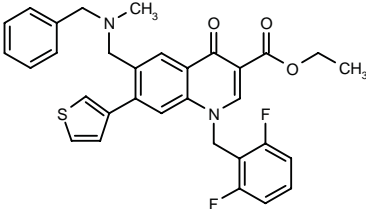
1. Bunnage, M.E. et al. (Pfizer Inc.;Pfizer Ltd.) *Pyrazolopyrimidinone cGMP PDE5 inhibitors for the treatment of sexual dysfunction*. EP 1073658, JP 2002512248, US 6251904, WO 9954333.

2. Bunnage, M.E. et al. *Design of potent and selective PDE5 inhibitors for treatment of MED*. 224th ACS Natl Meet (Aug 18-22, Boston) 2002, Abst MED1 2.

AGENTS FOR FEMALE INFERTILITY

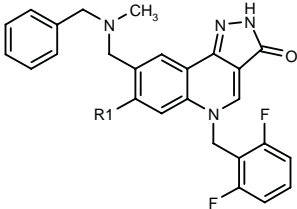
323023

6-(*N*-Benzyl-*N*-methylaminomethyl)-1-(2,6-difluorobenzyl)-4-oxo-7-(3-thienyl)-1,4-dihydroquinoline-3-carboxylic acid ethyl ester

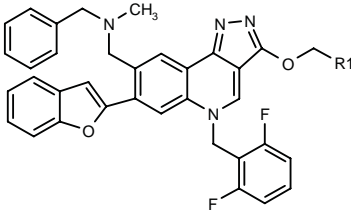


C32 H28 F2 N2 O3 S; Mol wt: 558.6462

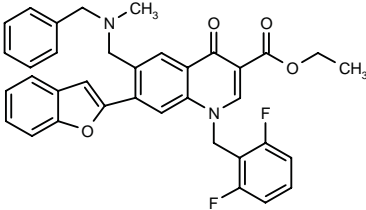
ACTION – Gonadotropin-releasing hormone (GnRH) antagonist proven to inhibit [³H]-histrelin binding to rat pituitary GnRH receptors with an IC₅₀ of 32 μM; it also exhibited antagonist activity in a luciferase reporter gene assay using HEK 293 cells (IC₅₀ = 10 μM). Potentially useful for the treatment of infertility, prostate cancer and benign prostatic hyperplasia, and also as a contraceptive agent. Other exemplified compounds are:



Compound	R1	Formula
323026	Br	C ₂₆ H ₂₁ BrF ₂ N ₄ O
323027	2-benzofuryl	C ₃₄ H ₂₆ F ₂ N ₄ O ₂



Compound	R1	Formula
323028	Ph	C ₄₁ H ₃₂ F ₂ N ₄ O ₂
323029	Me	C ₃₆ H ₃₀ F ₂ N ₄ O ₂



323024: C36 H30 F2 N2 O4

SOURCE – Ortho-McNeil.

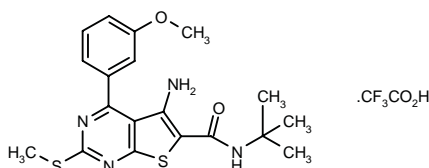
REFERENCES

1. Sui, Z. et al. (Ortho-McNeil Pharmaceutical, Inc.) *7-Heterocyclyl quinoline and thieno[2,3-b]pyridine derivs. useful as antagonists of gonadotropin releasing hormone*. WO 0248112.

ORG-41841*

295810

5-Amino-*N-tert*-butyl-4-(3-methoxyphenyl)-2-(methylsulfanyl)thieno[2,3-*d*]pyrimidine-6-carboxamide trifluoroacetate



C19 H22 N4 O2 S2 . C2 H F3 O2; Mol wt: 516.5627

ACTION – Orally active low-molecular-weight luteinizing hormone (LH) receptor agonist ($EC_{50} = 30$ nM in CHO cells stably expressing human LH receptors) able to induce ovulation in 40% of mice treated at a dose of 50 mg/kg p.o. Potentially useful for ovulation induction in infertility treatment in women.

SOURCE – Akzo Nobel.

REFERENCES

1. Gerritsma, G.G. et al. (Akzo Nobel N.V.) *Bicyclic heteroaromatic cpds. useful as LH agonists*. EP 1171443, WO 0061586.
2. Timmers, C.M. and Karstens, W.F.J. (Akzo Nobel N.V.) *Bicyclic heteroaromatic cpds*. WO 0224703.
3. van Straten, N.C.R. et al. *The first orally active low molecular weight agonists for the LH receptor: Thienopyr(im)idines with therapeutic potential*. Drugs Fut 2002, 27(Suppl. A): Abst C36.

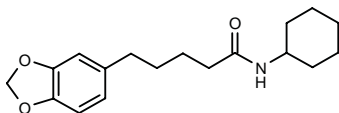
*Identified compound **295810** (see **295808**) Drug Data Rep 2001, 023(03): 0271.

DERMATOLOGIC DRUGS

RV-C04

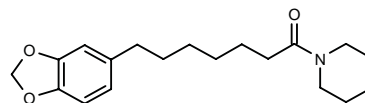
324586

5-(1,3-Benzodioxol-5-yl)-*N*-cyclohexylpentanamide



C18 H25 N O3; Mol wt: 303.3995

ACTION – Agent for the treatment of skin conditions, as indicated by its ability to concentration-dependently stimulate the proliferation of mouse melanocytes *in vitro*, and also to increase the dendricity of melanocytes. Potentially useful for the treatment of conditions requiring stimulation of melanocyte proliferation or inhibition of melanoma, such as vitiligo and skin cancer. Another exemplified compound is:



RV-C05 [324587]: C19 H27 N O3

SOURCE – BTG.

REFERENCES

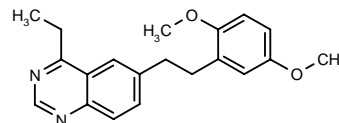
1. Hider, R.C. et al. (BTG International Ltd.) *Cpds. for use in the treatment of skin conditions*. WO 0257260.

SDZ-LAV-694*

283171

6-[2-(2,5-Dimethoxyphenyl)ethyl]-4-ethylquinazoline

LAV-694



C20 H22 N2 O2; Mol wt: 322.4058

ACTION – Topical antiproliferative agent, a lavendustin A derivative with improved solubility, *in vitro* and *in vivo* potency, metabolic stability and skin penetration compared to the parent compound SDZ-LAP-977. In pigs, topically applied, compound showed low systemic exposure, rapid systemic metabolic inactivation and excellent safety. Currently in phase I clinical trials for the treatment of actinic keratoses.

SOURCE – Novartis.

REFERENCES

1. Nussbaumer, P. (Novartis AG) *Trisubstd. phenyl derivs*. US 5990116, WO 9628430.
2. Nussbaumer, P. et al. *SDZ LAV 694: A novel antiproliferative agent for topical use*. Drugs Fut 2002, 27(Suppl. A): Abst C58.
3. Reinhardt, J. *Innovation and productivity drive sustained growth*. Novartis R&D Invest Semin (Dec 6, Basel) 2000.

*Identified compound **283171** Drug Data Rep 2000, 022(01): 0052.

SOURCE – Ortho-McNeil.

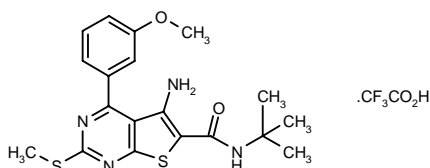
REFERENCES

1. Sui, Z. et al. (Ortho-McNeil Pharmaceutical, Inc.) *7-Heterocyclyl quinoline and thieno[2,3-b]pyridine derivs. useful as antagonists of gonadotropin releasing hormone*. WO 0248112.

ORG-41841*

295810

5-Amino-*N*-*tert*-butyl-4-(3-methoxyphenyl)-2-(methylsulfanyl)thieno[2,3-*d*]pyrimidine-6-carboxamide trifluoroacetate



C19 H22 N4 O2 S2 . C2 H F3 O2; Mol wt: 516.5627

ACTION – Orally active low-molecular-weight luteinizing hormone (LH) receptor agonist ($EC_{50} = 30$ nM in CHO cells stably expressing human LH receptors) able to induce ovulation in 40% of mice treated at a dose of 50 mg/kg p.o. Potentially useful for ovulation induction in infertility treatment in women.

SOURCE – Akzo Nobel.

REFERENCES

1. Gerritsma, G.G. et al. (Akzo Nobel N.V.) *Bicyclic heteroaromatic cpds. useful as LH agonists*. EP 1171443, WO 0061586.
2. Timmers, C.M. and Karstens, W.F.J. (Akzo Nobel N.V.) *Bicyclic heteroaromatic cpds*. WO 0224703.
3. van Straten, N.C.R. et al. *The first orally active low molecular weight agonists for the LH receptor: Thienopyr(im)idines with therapeutic potential*. Drugs Fut 2002, 27(Suppl. A): Abst C36.

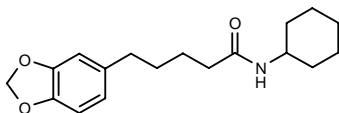
*Identified compound **295810** (see **295808**) Drug Data Rep 2001, 023(03): 0271.

DERMATOLOGIC DRUGS

RV-C04

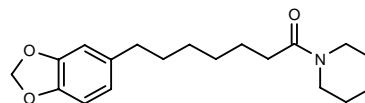
324586

5-(1,3-Benzodioxol-5-yl)-*N*-cyclohexylpentanamide



C18 H25 N O3; Mol wt: 303.3995

ACTION – Agent for the treatment of skin conditions, as indicated by its ability to concentration-dependently stimulate the proliferation of mouse melanocytes *in vitro*, and also to increase the dendricity of melanocytes. Potentially useful for the treatment of conditions requiring stimulation of melanocyte proliferation or inhibition of melanoma, such as vitiligo and skin cancer. Another exemplified compound is:



RV-C05 [324587]: C19 H27 N O3

SOURCE – BTG.

REFERENCES

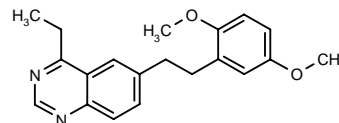
1. Hider, R.C. et al. (BTG International Ltd.) *Cpds. for use in the treatment of skin conditions*. WO 0257260.

SDZ-LAV-694*

283171

6-[2-(2,5-Dimethoxyphenyl)ethyl]-4-ethylquinazoline

LAV-694



C20 H22 N2 O2; Mol wt: 322.4058

ACTION – Topical antiproliferative agent, a lavendustin A derivative with improved solubility, *in vitro* and *in vivo* potency, metabolic stability and skin penetration compared to the parent compound SDZ-LAP-977. In pigs, topically applied, compound showed low systemic exposure, rapid systemic metabolic inactivation and excellent safety. Currently in phase I clinical trials for the treatment of actinic keratoses.

SOURCE – Novartis.

REFERENCES

1. Nussbaumer, P. (Novartis AG) *Trisubstd. phenyl derivs*. US 5990116, WO 9628430.
2. Nussbaumer, P. et al. *SDZ LAV 694: A novel antiproliferative agent for topical use*. Drugs Fut 2002, 27(Suppl. A): Abst C58.
3. Reinhardt, J. *Innovation and productivity drive sustained growth*. Novartis R&D Invest Semin (Dec 6, Basel) 2000.

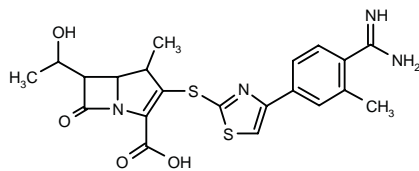
*Identified compound **283171** Drug Data Rep 2000, 022(01): 0052.

ANTIINFECTIVE THERAPY

ANTIBIOTICS

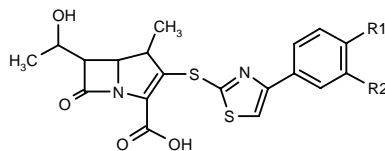
323011

2-[4-(4-Amidino-3-methylphenyl)thiazol-2-ylsulfany]-6-(1-hydroxyethyl)-1-methyl-1-carba-2-penem-3-carboxylic acid



C21 H22 N4 O4 S2; Mol wt: 458.5608

ACTION – Carbapenem antibiotic reportedly useful for the treatment of Gram-positive bacterial infections, particularly those caused by methicillin-resistant staphylococci. Other exemplified β -lactam compounds are:



Compound	R1	R2	Formula
323012	C(=NH)NH2	Br	C ₂₀ H ₁₉ BrN ₄ O ₄ S ₂
323013	C(=NH)NH2	OH	C ₂₀ H ₂₀ N ₄ O ₅ S ₂
323014	C(=NH)NH2	CH2NHSO2NH2	C ₂₁ H ₂₄ N ₆ O ₆ S ₃
323015	Br	C(=NH)NH2	C ₂₀ H ₁₉ BrN ₄ O ₄ S ₂
323016	OH	C(=NH)NH2	C ₂₀ H ₂₀ N ₄ O ₅ S ₂
323017	NHSO2NH2	C(=NH)NH2	C ₂₀ H ₂₂ N ₆ O ₆ S ₃
323019	H	C(=NMe)NHCH2CH2OH	C ₂₃ H ₂₆ N ₄ O ₅ S ₂
323020	5-OH-1,4,5,6-tetrahydro-2-pyrimidinyl	H	C ₂₃ H ₂₄ N ₄ O ₅ S ₂
323021	H	C(=NH)NHet	C ₂₂ H ₂₄ N ₄ O ₄ S ₂

SOURCE – Sumitomo Pharmaceuticals.

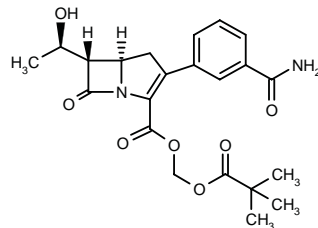
REFERENCES

1. Sunagawa, M. and Hebeisen, P. (Sumitomo Pharmaceuticals Co., Ltd.) *Novel β -lactam cpds. and process for preparing the same.* WO 0248149.

324270

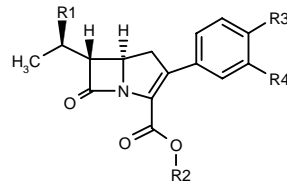
(5*R*,6*S*)-3-(3-Carbamoylphenyl)-6-[1(*R*)-hydroxyethyl]-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid 2,2-dimethylpropionyloxymethyl ester

(5*R*,6*S*)-2-(3-Carbamoylphenyl)-6-[1(*R*)-hydroxyethyl]-2-carbapenem-3-carboxylic acid 2,2-dimethylpropionyl-oxymethyl ester



C22 H26 N2 O7; Mol wt: 430.4544

ACTION – Carbapenem antibacterial agent reported to be active against a broad range of Gram-positive and Gram-negative bacteria, particularly penicillin-resistant *Staphylococcus pneumoniae* and resistant strains of *Haemophilus influenzae*. Other exemplified compounds are:



Compound	R1	R2	R3	R4	Formula
324272	OH	CH2OAc	CONHMe	H	C ₂₀ H ₂₂ N ₂ O ₇
324273	OH	t-BuCOOCH2	CONH2	Cl	C ₂₂ H ₂₅ FN ₂ O ₇
324274	OH	cyclohexyl-OCO2CH(Me)	H	CONHMe	C ₂₅ H ₃₀ N ₂ O ₈
324275	OH	H	CON(Me)2	H	C ₁₇ H ₁₈ N ₂ O ₅
324276	OH	t-BuCOOCH2	CH2OMe	CONH2	C ₂₄ H ₃₀ N ₂ O ₈
324277	OH	t-BuCOOCH2	1-Pip-CO	H	C ₂₇ H ₃₄ N ₂ O ₇
324278	H	t-BuCOOCH2	H	CONH2	C ₂₂ H ₂₆ N ₂ O ₆

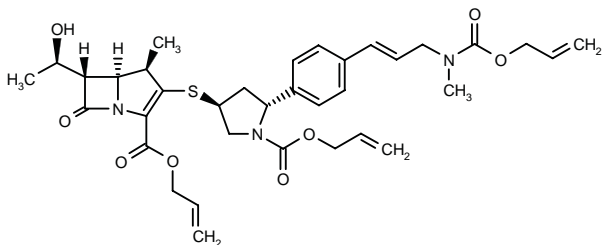
SOURCE – Sumitomo Pharmaceuticals.

REFERENCES

1. Sunagawa, M. and Sasaki, A. (Sumitomo Pharmaceuticals Co., Ltd.) *Novel carbapenem cpds.* WO 0253566.

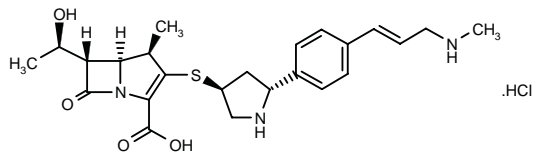
324517

(1*R*,5*S*,6*S*)-2-[1-(Allyloxycarbonyl)-5(*R*)-[4-[3-[*N*-(allyloxycarbonyl)-*N*-methylamino]-1-propenyl]phenyl]pyrrolidin-3(*S*)-ylsulfany]-6-[1(*R*)-hydroxyethyl]-1-methyl-1-carba-2-penem-3-carboxylic acid allyl ester



C35 H43 N3 O8 S; Mol wt: 665.8037

ACTION – Carbapenem antibacterial agent that displayed *in vitro* activity against *Staphylococcus aureus* BB5939 and *Staphylococcus epidermidis* BB5974 strains (MIC < 2 µg/ml). Another exemplified pyrrolidinyl-containing carbapenem derivative is:



324519: C24 H31 N3 O4 S . HCl

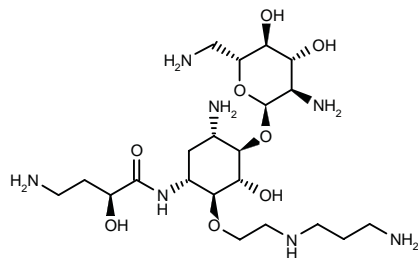
SOURCE – Banyu.

REFERENCES

1. Yamada, K. et al. (Banyu Pharmaceutical Co., Ltd.) *Novel carbapenem derivs.* JP 2002179679.

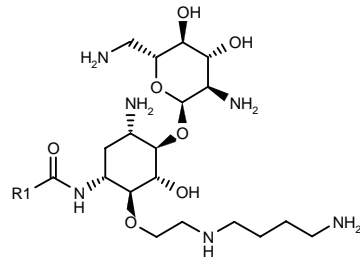
324678

4-Amino-*N*-[(1*R*,2*S*,3*R*,4*R*,5*S*)-5-amino-2-[2-(3-aminopropylamino)ethoxy]-4-(2,6-diamino-2,6-dideoxy-α-D-glucopyranosyloxy)-3-hydroxycyclohexyl]-2(*S*)-hydroxybutyramide



C21 H45 N7 O8; Mol wt: 523.6275

ACTION – Aminoglycoside antibiotic proven active *in vitro* against *Escherichia coli*, *Serratia marcescens*, *Enterobacter cloacae*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Enterococcus faecium* strains, with activity superior to neamine and kanamycin A. Compound was not affected by aminoglycoside-modifying enzymes. Other exemplified compounds are:



Compound	R1	Formula
324679	(<i>S</i>)-CH(OH)CH2CH2NH2	C22H47N7O8
324680	4-NH2-PhCH2	C26H47N7O7
324681	3-NH2-PhCH2	C26H47N7O7

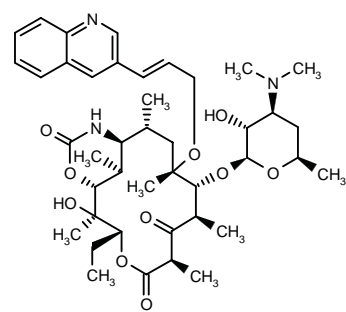
SOURCE – Wayne State University, Detroit, MI (US).

REFERENCES

1. Haddad, J. et al. (Wayne State University) *Aminoglycosides as antibiotics.* WO 0257281.

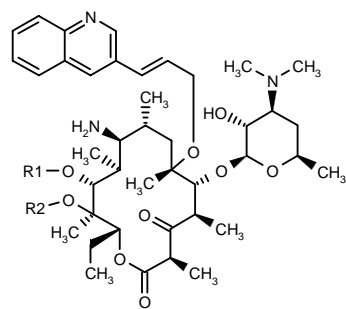
324684

9-Amino-9-deoxo-3-des(hexopyranosyloxy)-3-oxo-6-*O*-[3-(3-quinolinyl)-2-propenyl]erythromycin A 9-*N*,11-*O*-cyclic carbamate

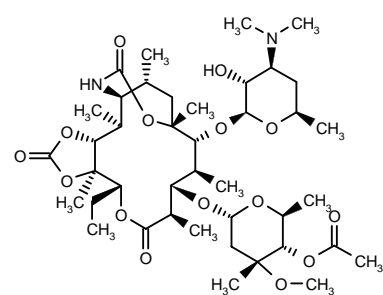


C42 H61 N3 O10; Mol wt: 767.9549

ACTION – Antibacterial erythromycin derivative demonstrating *in vitro* activity against *Staphylococcus aureus* ATCC 6538P (MIC = 0.39 µg/ml), *Haemophilus influenzae* DILL AMP R (MIC = 16 µg/ml), *Streptococcus pyogenes* EES61 (MIC = 0.03 µg/ml), *S. pyogenes* PIU 2548 (MIC = 1 µg/ml), *Streptococcus pneumoniae* ATCC 6303 (MIC = 0.03 µg/ml) and *S. pneumoniae* 5649 (MIC = 2 µg/ml). Other exemplified 9-aminoerythromycin A derivatives are:



Compound	R1	R2	Formula
324686	H	H	C41H63N3O9
324687	-CO-		C42H61N3O10



324685: C41 H68 N2 O15

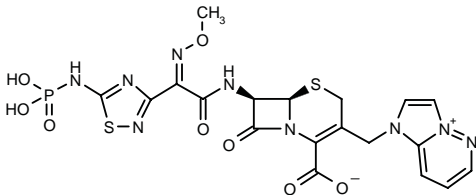
SOURCE – Abbott.

REFERENCES

1. Ma, Z. et al. (Abbott Laboratories) *9-Amino erythromycin derivs. with anti-bacterial activity.* WO 0257286.

324816

3-(1*H*-Imidazo[1,2-*b*]pyridazin-4-ium-1-ylmethyl)-7(*R*)-[(*Z*)-2-(methoxyimino)-2-[5-(phosphonoamino)-1,2,4-thiadiazol-3-yl]acetamido]-3-cephem-4-carboxylate inner salt



C19 H18 N9 O8 P S2; Mol wt: 595.5122

ACTION – A representative compound from a series of phosphono-substituted cephem derivatives with anti-bacterial activity, proven able to prevent infections caused by *Staphylococcus aureus* 308A-1 and *Pseudomonas aeruginosa* P9 in mice with ED₅₀ values of 2.51 and 0.91 mg/kg s.c., respectively.

SOURCE – Takeda.

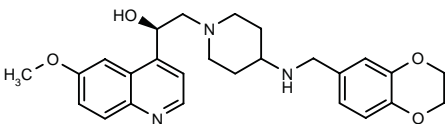
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ANTIBACTERIAL DRUGS

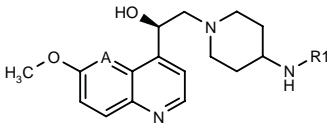
324507

2-[4-(2,3-Dihydro-1,4-benzodioxin-6-ylmethylamino)-piperidin-1-yl]-1(*R*)-(6-methoxyquinolin-4-yl)ethanol



C26 H31 N3 O4; Mol wt: 449.5479

ACTION – Antibacterial agent possessing *in vitro* activity against *Staphylococcus aureus* Oxford, *S. aureus* WCUH29, *Streptococcus pneumoniae* 1629, *S. pneumoniae* N1387, *S. pneumoniae* ERY 2, *Haemophilus influenzae* Q1 and *Enterococcus faecalis* 1. Other exemplified compounds are:



Compound	R1	A	Formula
324508	3-oxo-3,4-dihydro-2H-1,4-benzothiazin-6-yl-CH2	CH	C ₂₆ H ₃₀ N ₄ O ₃ S
324509	6-NO2-1,3-benzodioxol-5-yl-CH2	CH	C ₂₅ H ₂₈ N ₄ O ₆
324510	2,3-dihydro-1,4-dioxino-[2,3- <i>b</i>]pyridin-6-yl-CH2	CH	C ₂₅ H ₃₀ N ₄ O ₄
324511	7-F-3-oxo-3,4-dihydro-2H-1,4-benzothiazin-6-yl-CH2	N	C ₂₅ H ₂₈ FN ₅ O ₃ S
324512	2,3-dihydro-1,4-dioxino-[2,3- <i>b</i>]pyridin-7-yl-CH2	CH	C ₂₅ H ₃₀ N ₄ O ₄
324513	3-oxo-3,4-dihydro-2H-pyrido[3,2- <i>b</i>]-1,4-thiazin-6-yl-CO	CH	C ₂₅ H ₂₇ N ₅ O ₄ S

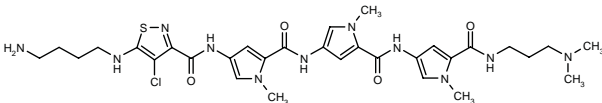
SOURCE – GlaxoSmithKline.

REFERENCES

1. Davies, D.T. et al. (GlaxoSmithKline plc) *Quinolines and nitrogenated deriv. thereof substd. in 4-position by a piperidine-containing moiety and their use as antibacterial agents*. WO 0256882.

324770

5-(4-Aminobutylamino)-4-chloro-*N*-[5-[*N*-[5-[*N*-[5-[*N*-[3-(dimethylamino)propyl]carbamoyl]-1-methyl-1*H*-pyrrol-3-yl]carbamoyl]-1-methyl-1*H*-pyrrol-3-yl]carbamoyl]-1-methyl-1*H*-pyrrol-3-yl]isothiazole-3-carboxamide



C31 H42 Cl N11 O4 S; Mol wt: 700.2648

ACTION – Antibacterial agent, a DNA minor groove-binding ligand (K_d = 1.04 nM) with strong antibacterial activity against drug-resistant Gram-positive bacteria including methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus faecalis* and penicillin-resistant *Streptococcus pneumoniae* (MIC = 2, 1 and 1 µg/ml, respectively). It was also active against *Candida albicans* (MIC = 8 µg/ml). *In vivo* compound (2-10 mg/kg i.p.) significantly prolonged the life span of *S. aureus*-infected mice.

SOURCE – GeneSoft.

REFERENCES

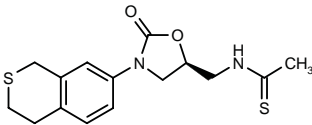
1. Ge, Y. et al. (GeneSoft, Inc.) *Charged cpds. comprising a nucleic acid binding moiety and uses therefor*. WO 0174898.

2. Bürli, R.W. et al. *DNA binding ligands with excellent antibiotic potency against drug-resistant Gram-positive bacteria*. Bioorg Med Chem Lett 2002, 12(18): 2591.

3. Bürli, R.W. et al. *DNA minor groove binding ligands with excellent potency against drug-resistant Gram-positive bacteria*. Drugs Fut 2002, 27(Suppl. A): Abst P159.

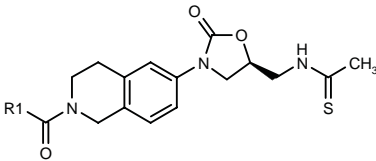
324972

(+)-N-[3-(3,4-Dihydro-1*H*-2-benzothiopyran-7-yl)-2-oxooxazolidin-5(*S*)-ylmethyl]thioacetamide

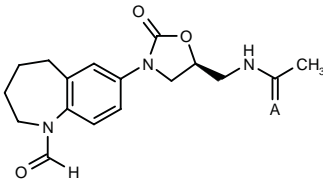


C15 H18 N2 O2 S2; Mol wt: 322.4512

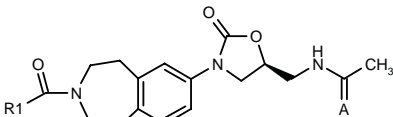
ACTION – Oxazolidinone antibacterial agent that displayed an MIC value of 0.125 µg/ml against *Streptococcus pneumoniae* 9912. Other exemplified compounds are:



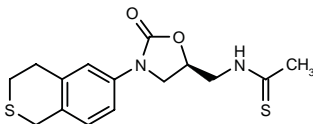
Compound	R1	Formula
324975	OMe	C ₁₇ H ₂₁ N ₃ O ₄ S
324976	H	C ₁₆ H ₁₉ N ₃ O ₃ S
324977	CH2OH	C ₁₇ H ₂₁ N ₃ O ₄ S



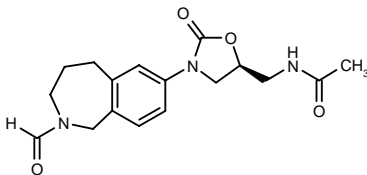
Compound	A	Formula
324979	O	C ₁₇ H ₂₁ N ₃ O ₄
324980	S	C ₁₇ H ₂₁ N ₃ O ₃ S



Compound	R1	A	Formula
324981	OCH2Ph	O	C ₂₄ H ₂₇ N ₃ O ₅
324982	H	O	C ₁₇ H ₂₁ N ₃ O ₄
324983	CH2OH	O	C ₁₈ H ₂₃ N ₃ O ₅
324988	CH2OH	S	C ₁₈ H ₂₃ N ₃ O ₄ S



324978:C15 H18 N2 O2 S2



324986:C17 H21 N3 O4

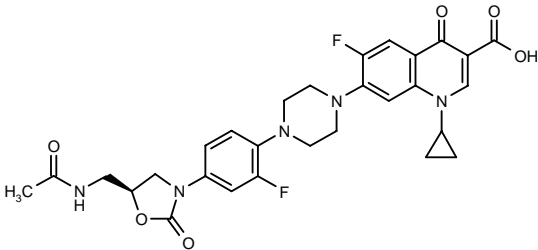
SOURCE – Pharmacia.

REFERENCES

1. Johnson, P.D. et al. (Pharmacia Corp.) *Oxazolidinones having a benzannulated 6- or 7-membered heterocycle as antibacterial agents*. WO 0259115.

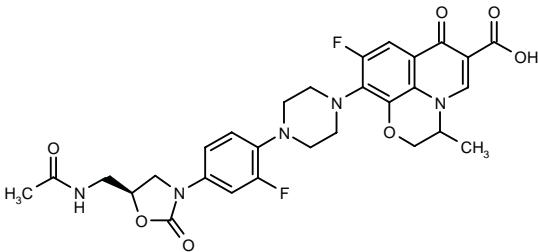
324984

7-[4-[4-[5(*S*)-(Acetamidomethyl)-2-oxooxazolidin-3-yl]-2-fluorophenyl]piperazin-1-yl]-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid

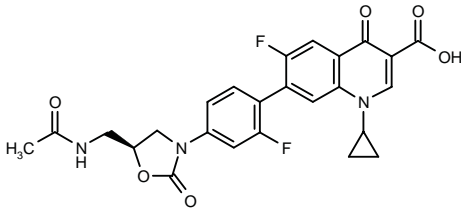


C29 H29 F2 N5 O6; Mol wt: 581.5731

ACTION – Antibacterial quinolone that showed *in vitro* activity against *Enterococcus faecalis* UC9217 (MIC = 0.25 µg/ml), *Staphylococcus aureus* UC9218 (MIC = 0.5 µg/ml), *Streptococcus pneumoniae* UC9912 (MIC = 0.125 µg/ml), *Haemophilus influenzae* UC30063 (MIC = 8 µg/ml), *Moraxella catarrhalis* UC30607 (MIC = 1 µg/ml) and *Escherichia coli* UC6674 (MIC = 16 µg/ml). Other exemplified compounds are:



324985: C29 H29 F2 N5 O7



324987: C25 H21 F2 N3 O6

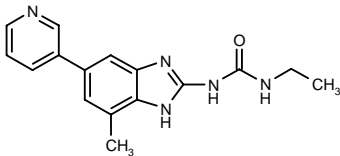
SOURCE – Pharmacia.

REFERENCES

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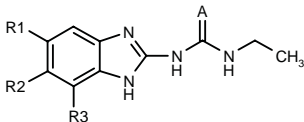
325332

N-Ethyl-N'-[7-methyl-5-(3-pyridyl)-1 H-benzimidazol-2-yl]-urea



C16 H17 N5 O; Mol wt: 295.3443

ACTION – Bacterial gyrase inhibitor (> 75% inhibition of *Staphylococcus aureus* enzyme at 10 μM) with anti-bacterial activity (MIC < 10 μg/ml), potentially useful for the treatment of bacterial infections, particularly those caused by *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Enterococcus faecalis*, *Enterococcus faecium*, *Klebsiella pneumoniae*, *Enterobacter* spp., *Proteus* spp., *Pseudomonas aeruginosa*, *Escherichia coli*, *Serratia marcesens*, *Staphylococcus aureus* and coagulase-negative staphylococci. Other exemplified compounds are:



Compound	R1	R2	R3	A	Formula
325334	Ph	H	H	S	C ₁₆ H ₁₆ N ₄ S
325335	2-MeS-5-pyrimidinyl	H	H	O	C ₁₅ H ₁₆ N ₆ OS
325336	2-MeO-5-pyrimidinyl	OMe	H	O	C ₁₆ H ₁₈ N ₆ O ₃
325337	3-Pyr	H	H	O	C ₁₅ H ₁₅ N ₅ O
325338	3-Pyr	Me	H	O	C ₁₆ H ₁₇ N ₅ O
325340	2-[MeOCH2CH(Me)O]-5-pyrimidinyl	OMe	H	O	C ₁₉ H ₂₄ N ₆ O ₄
325341	2-[MeOCH2CH(Me)NH]-5-pyrimidinyl	OMe	H	O	C ₁₉ H ₂₅ N ₇ O ₃
325342	6-EtO-3-Pyr	H	H	O	C ₁₇ H ₁₉ N ₅ O ₂
325343	3-Pyr	H	OCH2Ph	O	C ₂₂ H ₂₁ N ₅ O ₂
325344	4-(BuNHCO)-1-imidazolyl	H	H	O	C ₁₈ H ₂₃ N ₇ O ₂

SOURCE – Vertex.

REFERENCES

1. Grillot, A.-L. et al. (Vertex Pharmaceuticals Inc.) *Gyrase inhibitors and uses thereof*. WO 0260879.

ACIDFORM™

321981

Acid-buffering (pH 3.55) bioadhesive vaginal gel consisting of gelling agents, buffer salts, humectants, preservatives and water in a proprietary mixture

ACTION – Microbicidal and spermicidal agent, an acid-buffering bioadhesive vaginal gel with improved acid-buffering and bioadhesive properties and viscosity compared to other commercially available vaginal microbicides. *In vitro* experiments demonstrated that the gel inhibited the growth of a number of anaerobes associated with bacterial vaginitis including *Gardnerella vaginalis* and *Trichomonas vaginalis*. Results of a phase I clinical trial showed that the gel is safe and did not induce vaginal or cervical irritation after application for 6 days.

SOURCES – AO Pharmaceutico; Universidade Estadual de Campinas, Campinas (BR); University of Illinois at Chicago, Chicago, IL (US); Rush Presbyterian St. Luke’s Medical Center, Chicago, IL (US); US Department of Health & Human Services (US).

REFERENCES

1. Amaral, E. et al. *Post-coital testing and vaginal ecology after use of a bio-adhesive acid buffering gel (ACIDFORM) and a 2% nonoxynol-9 product*. Microbicides (May 12-15, Antwerp) 2002, Abst B-136.

2. Amaral, E. et al. *Study of the vaginal tolerance to Acidform, an acid-buffering, bioadhesive gel*. Contraception 1999, 60(6): 361.

3. Garg, S. et al. *Properties of a new acid-buffering bioadhesive vaginal formulation (ACIDFORM)*. Contraception 2001, 64(1): 67.

4. Kandarapu, R. et al. *Development of acid-buffering tablets as novel microbicide: Comparative evaluation with ACIDFORM gel*. Microbicides (May 12-15, Antwerp) 2002, Abst A-147.

5. Olmsted, S.S. et al. *Mild acidity immobilizes and kills human leukocytes*. Microbicides (May 12-15, Antwerp) 2002, Abst A-177.

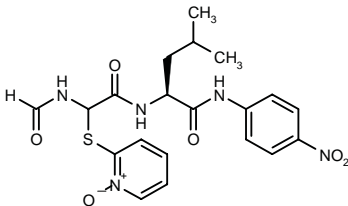
6. Tevi-Benissan, C. et al. *ACIDFORM: An acid-buffering and bio-adhesive gel with activity against bacterial vaginosis and Trichomonas vaginalis in vitro*. 14th Int AIDS Conf (July 7-12, Barcelona) 2002, Abst MoPeD3659.

NB-002072

323633

N²-[2-Formamido-2-(1-oxidopyridin-2-ylsulfanyl)acetyl]-N¹-(4-nitrophenyl)-L-leucinamide

NB-2072



C20 H23 N5 O6 S; Mol wt: 461.4967

ACTION – Broad-spectrum antibacterial agent, a small N-formyl peptidomimetic that mimics the essential bacterial enzyme peptide deformylase and is designed to release a potent toxin incorporated into the α position by catalytic deformylation, followed by α elimination within the diseased cells.

SOURCE – NewBiotics.

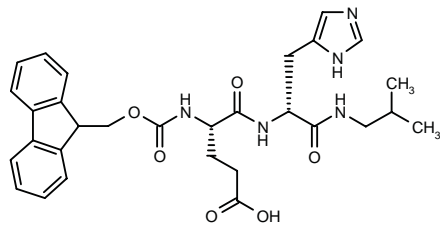
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PTX-042695

323855

N-(9*H*-Fluoren-9-ylmethoxycarbonyl)-L-glutamyl-D-histidine isobutylamide



C30 H35 N5 O6; Mol wt: 561.6355

ACTION – Potential antibacterial agent, a potent inhibitor of phosphopantetheine adenyllyltransferase (PPAT; IC₅₀ = 6 nM against *Escherichia coli* PPAT).

SOURCE – Pantherix.

REFERENCES

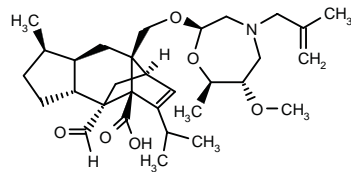
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ANTIFUNGAL AGENTS

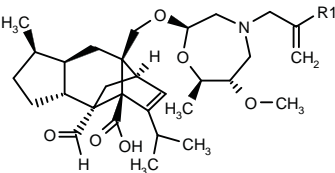
322899

(1*R*,3*aR*,4*S*,4*aR*,7*R*,7*aR*,8*aS*)-4-Formyl-3-isopropyl-8a-[(2*R*,6*S*,7*R*)-6-methoxy-7-methyl-4-(2-methyl-2-propenyl)perhydro-1,4-oxazepin-2-yl]oxymethyl]-7-methyl-4,4*a*,5,6,7,7*a*,8,8*a*-octahydro-1*H*-1,4-methano-*s*-indacene-3*a*-carboxylic acid



C31 H47 N O6; Mol wt: 529.7133

ACTION – Antifungal agent, a sordaricin analogue with broad-spectrum antifungal activity against *Candida albicans* including strains with low azole susceptibility (MIC = 0.016-0.25 µg/ml); it was inactive against *Candida parapsilosis* and *Aspergillus fumigatus*. The antifungal activity was retained in the presence of medium supplemented with 20% horse serum (MIC = 0.25-0.5 µg/ml). Other related compounds are:



Compound	R1	Formula
324418	Cl	C ₃₀ H ₄₄ ClNO ₆
324419	Br	C ₃₀ H ₄₄ BrNO ₆

SOURCE – Sankyo.

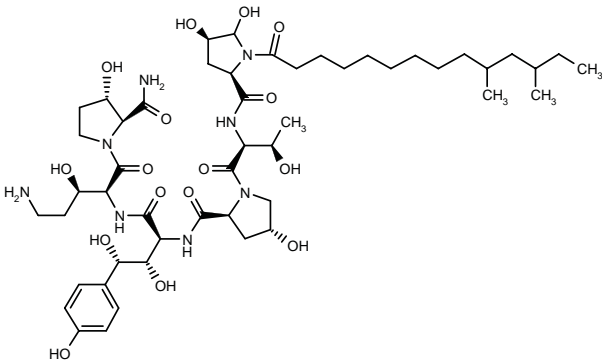
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2. Kaneko, S. et al. *Synthesis and evaluation of N-substituted 1,4-oxazepanyl sordaricins as selective fungal EF-2 inhibitors*. Bioorg Med Chem Lett 2002, 12(13): 1705.

324465

1-(10,12-Dimethyltetradecanoyl)-4(*R*),5-dihydroxy-D-prolyl-L-threonyl-4(*R*)-hydroxy-L-prolyl-4(*S*)-hydroxy-4-(4-hydroxyphenyl)-L-threonyl-3(*R*)-hydroxy-L-ornithyl-3(*S*)-hydroxy-L-prolinamide



C50 H82 N8 O16; Mol wt: 1051.2380

ACTION – Active metabolite of the antifungal agent caspofungin⁺ with *in vitro* activity against *Candida albicans*, *Candida tropicalis*, *Candida krusei* and *Aspergillus fumigatus* strains; it also displayed *in vivo* efficacy in mice infected with *C. albicans* MY 1055.

SOURCE – Merck & Co.

REFERENCES

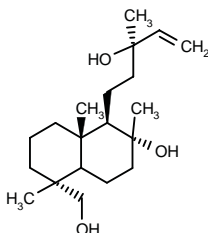
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⁺Drug Data Rep 2001, 023(04): 0375.

BC-3

324752

(1*R*,2*R*,5*R*,8*aS*)-5-(Hydroxymethyl)-1-[3(*R*)-hydroxy-3-methyl-4-pentenyl]-2,5,8*a*-trimethylperhydronaphthalen-2-ol



C20 H36 O3; Mol wt: 324.5014

ACTION – A representative compound from a series of naphthalene derivatives with antifungal activity, displaying IC₈₀ values of 16 and 1 µg/ml, respectively, against *Aspergillus fumigatus* and *Candida albicans* strains. *In vivo*, it exhibited a protective effect when orally administered to *A. fumigatus*-infected mice, affording a survival rate of at least 60% at doses of 10 and 2 mg/kg/day for 7 days.

SOURCE – Toagosei.

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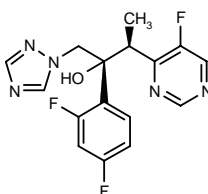
VORICONAZOLE⁺

Prop INN; BAN

179738

(2*R*,3*S*)-2-(2,4-Difluorophenyl)-3-(5-fluoropyrimidin-4-yl)-1-(1,2,4-triazol-1-yl)butan-2-ol

UK-109496



C16 H14 F3 N5 O; Mol wt: 349.3146

ACTION – Triazole antifungal agent for parenteral and oral administration.

INDICATION – Treatment of serious systemic fungal infections including cryptococcosis and acute invasive aspergillosis.

PRESENTATION – Tablets, 50 and 200 mg; vials containing lyophilized powder, 200 mg voriconazole, for i.v. infusion.

PROPRIETARY NAME – Vfend (US).

SOURCE – Pfizer.

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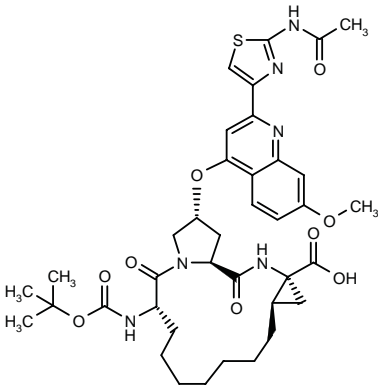
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ANTIVIRAL DRUGS

324392

(2*R*,6*S*,13*aR*,14*aR*,16*aS*)-2-[2-(2-Acetamidothiazol-4-yl)-7-methoxyquinolin-4-yloxy]-6-(*tert*-butoxycarbamido)-5,16-dioxohexadecahydrocyclopropa[*e*]pyrrolo[1,2-*a*]-[1,4]diazacyclopentadecine-14*a*(5*H*)-carboxylic acid



C38 H48 N6 O9 S; Mol wt: 764.8962

ACTION – Antiviral agent, a potent and competitive inhibitor of hepatitis C virus (HCV) NS3 serine protease (IC₅₀ = 0.006 μM) with high selectivity over other serine and cysteine proteases. It strongly inhibited HCV RNA replication in Huh-7 cells (EC₅₀ = 0.011 μM) and was orally bioavailable in rats (46%), dogs (20%) and monkeys (11%).

SOURCE – Boehringer Ingelheim.

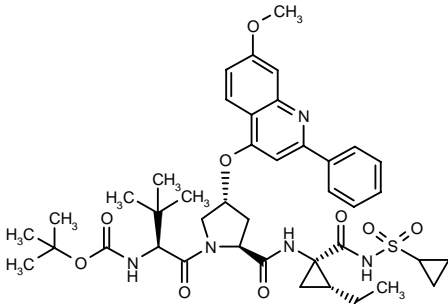
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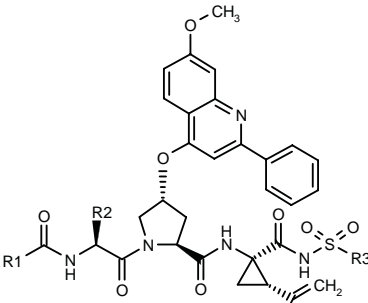
325359

1-[*N*-(*tert*-Butoxycarbonyl)-3-methyl-L-valyl]-*N*-[1(*R*)-[*N*-(cyclopropylsulfonyl)carbamoyl]-2(*R*)-ethylcyclopropyl]-4(*R*)-(7-methoxy-2-phenylquinolin-4-yloxy)-L-prolinamide



C41 H53 N5 O9 S; Mol wt: 791.9617

ACTION – Antiviral agent, an inhibitor of hepatitis C virus (HCV) NS3 serine protease (IC₅₀ < 0.05 μM) shown to prevent HCV replication in a whole-cell assay. Other exemplified compounds are:



Compound	R1	R2	R3	Formula
325362	3(R)-THF-O	t-Bu	cyclopropyl	C ₄₁ H ₄₉ N ₅ O ₁₀ S
325364	t-BuO	cyclopentyl	cyclopropyl	C ₄₂ H ₅₁ N ₅ O ₉ S
325369	t-BuO	t-Bu	Ph	C ₄₄ H ₅₁ N ₅ O ₉ S
325371	t-BuO	t-Bu	3-Br-Ph	C ₄₄ H ₅₀ BrN ₅ O ₉ S
325372	t-BuO	i-Pr	cyclobutyl	C ₄₁ H ₅₁ N ₅ O ₉ S
325374	t-BuCH2	t-Bu	cyclopropyl	C ₄₂ H ₅₃ N ₅ O ₈ S
325376	OPh	t-Bu	cyclopropyl	C ₄₃ H ₄₇ N ₅ O ₉ S
325377	OBu	t-Bu	cyclopropyl	C ₄₁ H ₅₁ N ₅ O ₉ S

SOURCE – Bristol-Myers Squibb.

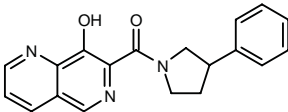
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AIDS MEDICINES

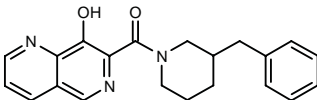
324260

1-(8-Hydroxy-1,6-naphthyridin-7-yl)-1-(3-phenylpyrrolidin-1-yl)methanone



C19 H17 N3 O2; Mol wt: 319.3623

ACTION – Agent with the ability to inhibit HIV integrase, potentially useful for the treatment or prevention of AIDS. Another compound within this series of aza- and polyaza-naphthalenyl carboxamides is:



324261: C21 H21 N3 O2

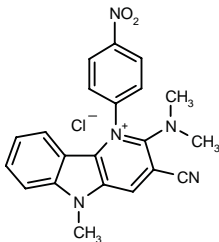
SOURCE – Merck & Co.

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324957

3-Cyano-2-(dimethylamino)-5-methyl-1-(4-nitrophenyl)-5*H*-pyrido[3,2-*b*]indol-1-ium chloride



C21 H18 Cl N5 O2; Mol wt: 407.8592

ACTION – Antiretroviral agent giving an IC₅₀ of 9.7 μM against HIV-1 reverse transcriptase (RT), and proven active against a panel of HIV-1, HIV-2 and SIV strains, with IC₅₀ values in the low nanomolar range.

SOURCE – US Department of Health & Human Services (US).

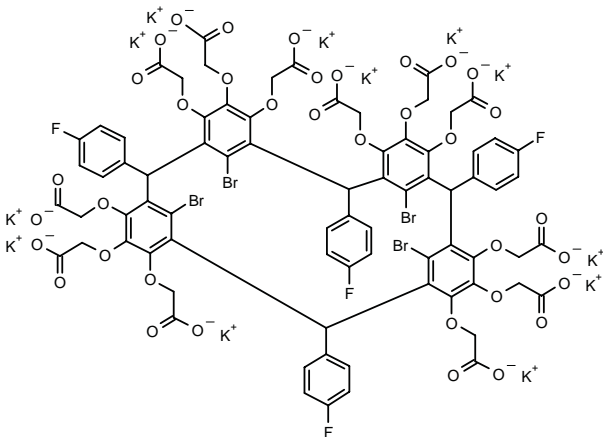
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AC-1

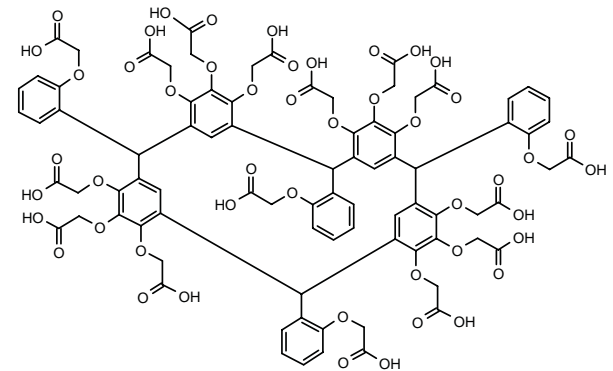
322409

25,26,27,28-Tetrabromo-4,5,6,10,11,12,16,17,18,22,23,24-dodecakis(carboxymethoxy)-2,8,14,20-tetrakis(4-fluorophenyl)pentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacos-1(25),3(28),4,6,9(27),10,12,15(26),16,18,21,23-dodecaene dodecakis potassium salt



C76 H44 Br4 F4 K12 O36; Mol wt: 2397.9320

ACTION – Antiviral agent that inhibits HIV fusion and integrase, with an IC₅₀ of 14.3 μM against HIV integrase; it was found to prevent HIV infectivity in C8166 cells with an IC₅₀ of 0.1 μM, while showing a TC₅₀ of 400 μM (therapeutic index TI = 4,000). Compound demonstrated an additive effect with zidovudine *in vitro*. When orally administered to patients with advanced disease at a dose of 500 mg/day, AC-1 was shown to induce a 100-fold decrease in viral load and a significant increase in CD4-expressing cells, indicative of improved immune status. In addition, a reduced incidence of opportunistic infections and an improvement in physical fitness (as measured by the Karnofsky score) were observed. Another exemplified macrocyclic compound is:



AC-2 [322410]: C84 H72 O48

SOURCE – AIDS Care Pharma.

REFERENCES

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PE_{HRG-214}

322052

Preparation containing purified polyclonal IgG antibodies to nonmutating and functionally important regions of HIV

ACTION – HIV-1 passive immunotherapy, a polyclonal antibody preparation that contains IgG antibodies to nonmutating and functionally important regions of HIV that are not recognized by the human immune system. It exhibited high affinity for multiple HIV epitopes and a broad spectrum of activity against primary HIV isolates. Results of a recently completed phase I dose-escalation trial in HIV-1-infected patients showed that single doses of 1, 2, 4, 8 and 16 mg/kg i.v. were generally well tolerated, the major adverse event being mild to moderate transient rash in half of the patients. At the higher dose, peak plasma levels exceeded those inhibiting all strains of virus *in vitro*.

SOURCE – Virionyx.

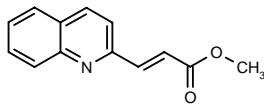
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TREATMENT OF PROTOZOAL DISEASES

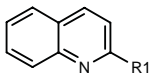
324582

3-(2-Quinoliny)-2(E)-propenoic acid methyl ester



C13 H11 N O2; Mol wt: 213.2349

ACTION – Agent for the treatment of protozoal infections caused by *Leishmania*, *Trypanosoma*, *Plasmodium*, *Toxoplasma*, *Pneumocystis* and *Schistosoma* micro-organisms, as well as retroviral infections caused by HIV and HTLV-1. Compound demonstrated *in vitro* activity against a panel of *Leishmania* and *Trypanosoma* strains. It also reduced the infectivity of *Leishmania amazonensis* and *Leishmania infantum* following oral administration to mice (25 mg/kg/day for 15 and 10 days, respectively). Other exemplified quinoline derivatives are:



Compound	R1	Formula
324583	ethynyl	C ₁₁ H ₇ N
324584	(E)-CH=CH <i>Et</i>	C ₁₃ H ₁₃ N
324585	(E)-CH=CHCHO	C ₁₂ H ₉ NO

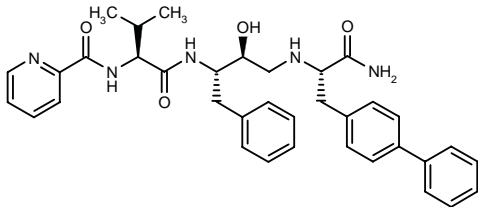
SOURCES – CNRS; Institut de Recherche pour le Développement, Paris (FR).

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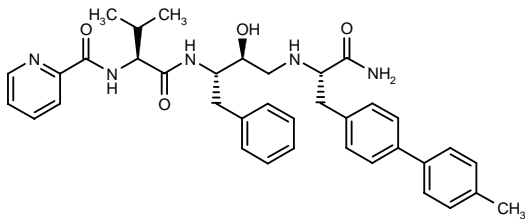
324747

*N*¹-[3-[2-Amino-1 (*S*)-(biphenyl-4-ylmethyl)-2-oxoethyl-amino]-1 (*S*)-benzyl-2 (*S*)-hydroxypropyl]-*N*²-(pyridin-2-ylcarbonyl)-L-valinamide



C36 H41 N5 O4; Mol wt: 607.7509

ACTION – Antimalarial agent, an inhibitor of plasmepsin I and II (*K*_i = 68 and 120 nM, respectively) with high selectivity over cathepsin D (*K*_i > 2000 nM). It inhibited *Plasmodium falciparum* growth in infected erythrocytes by 77% at 5 μM. Its properties in a Caco-2 cell penetration assay suggested oral bioavailability. Another related compound is:



324748: C37 H43 N5 O4

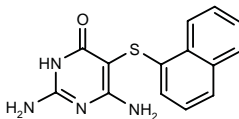
SOURCE – Uppsala University, Uppsala (SE).

REFERENCES

1. Nöteberg, D. et al. *New antimalarials: Design and synthesis of protease inhibitors with effect in cultured parasite-infected human erythrocytes*. Drugs Fut 2002, 27(Suppl. A): Abst P399.

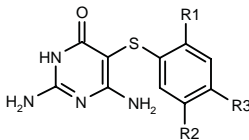
324754

2,6-Diamino-5-(naphthalen-1-ylsulfanyl)pyrimidin-4(3*H*)-one



C14 H12 N4 O S; Mol wt: 284.3418

ACTION – Dihydrofolate reductase (DHFR) and thymidylate synthase (TS) inhibitor giving an IC₅₀ of 0.49 μM against DHFR from *Toxoplasma gondii* and exhibiting 200-fold selectivity over rat liver DHFR. Potentially useful for the treatment of cancer, as well as bacterial, myco-bacterial, fungal and protozoal infections in immunocompromised patients. Other exemplified pyrimidine compounds are:



Compound	R1	R2	R3	Formula
324755	H	H	Cl	C ₁₀ H ₉ ClN ₄ OS
324756	H	OMe	H	C ₁₁ H ₁₂ N ₄ O ₂ S
324757	H	H	CO ₂ H	C ₁₁ H ₁₀ N ₄ O ₃ S
324758	OMe	OMe	H	C ₁₂ H ₁₄ N ₄ O ₃ S

SOURCE – Duquesne University, Pittsburgh, PA (US).

REFERENCES

1. Gangjee, A. (Duquesne University) *Pyrimidine cpds. and methods for making and using the same*. US 6423720.

WR-279396

323753

Formulation of aminoglycosides containing paromomycin (15%) and gentamicin (0.5%) in a complex hydrophilic base

ACTION – Topical antileishmanial agent, a combination of paromomycin and gentamicin with improved efficacy compared to the single components against murine cutaneous leishmaniasis. A formulation of compound containing 15% paromomycin and 0.5% gentamicin was evaluated in a phase II clinical trial in patients with cutaneous *Leishmania panamensis*; the cure rates for patients treated with compound and placebo were 61 and 55%, respectively; the mean cure times were 35 days for the drug-treated group and 56 days for the placebo group. No local or systemic side effects were observed.

SOURCE – Walter Reed Army Institute, Washington, DC (US).

REFERENCES

1. Grogl, M. et al. (Department of the Army) *Antileishmanial compsn. for topical application*. WO 9406439.

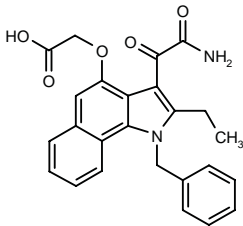
2. Grogl, M. et al. *Successful topical treatment of murine cutaneous leishmaniasis with a combination of paromomycin (Aminosidine) and gentamicin*. J Parasitol 1999, 85(2): 354.

3. Soto, J.M. et al. *Treatment of cutaneous leishmaniasis with a topical antileishmanial drug (WR279396): Phase 2 pilot study*. Am J Trop Med Hyg 2002, 66(2): 147.

TREATMENT OF SEPTIC SHOCK

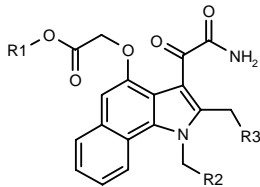
324597

2-(1-Benzyl-2-ethyl-3-oxamoyl-1 H-benzo[g]indol-4-yloxy)acetic acid



C25 H22 N2 O5; Mol wt: 430.4578

ACTION – Inhibitor of nonpancreatic secretory phospholipase A₂ (sPLA₂; IC₅₀ = 0.010 μM), potentially useful for the treatment of inflammatory diseases including sepsis, inflammatory bowel disease, adult respiratory distress syndrome, pancreatitis, asthma, allergic rhinitis, arthritis, cystic fibrosis, stroke, bronchitis, gout, etc. Other exemplified compounds are:



Compound	R1	R2	R3	Formula
324598	Me	Ph	Me	C ₂₆ H ₂₄ N ₂ O ₅
324599	Me	cyclohexyl	H	C ₂₅ H ₂₈ N ₂ O ₅
324600	H	cyclohexyl	H	C ₂₄ H ₂₆ N ₂ O ₅
324601	Me	3-(4-F-Ph)-Ph	H	C ₃₁ H ₂₅ FN ₂ O ₅
324603	H	3-(4-F-Ph)-Ph	H	C ₃₀ H ₂₃ FN ₂ O ₅

SOURCE – Lilly.

REFERENCES

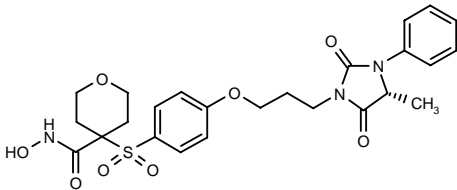
1. Bight, D.W. et al. (Eli Lilly and Company) *Novel sPLA2 inhibitors*. WO 0257231.

TREATMENT OF MUSCULOSKELETAL AND CONNECTIVE TISSUE DISEASES

ANTIARTHRITIC DRUGS

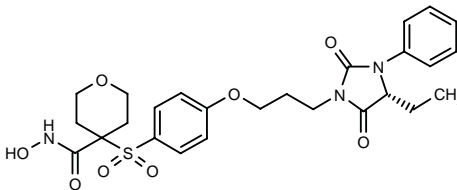
324003

4-[4-[3-[4(R)-Methyl-2,5-dioxo-3-phenylimidazolidin-1-yl]-propoxy]phenylsulfonyl]tetrahydro-2 H-pyran-4-carboxylic acid



C25 H29 N3 O8 S; Mol wt: 531.5831

ACTION – Potent collagenase 3 (MMP-13) inhibitor (IC₅₀ = 2.0 nM) with high selectivity over gelatinase A (MMP-2), neutrophil collagenase (MMP-8), gelatinase B (MMP-9) and interstitial collagenase (MMP-1) (IC₅₀ = 817, 1414, 9438 and > 10,000 nM, respectively). Potentially useful for the treatment of arthritis. Another related compound is:



324004: C26 H31 N3 O8 S

WR-279396

323753

Formulation of aminoglycosides containing paromomycin (15%) and gentamicin (0.5%) in a complex hydrophilic base

ACTION – Topical antileishmanial agent, a combination of paromomycin and gentamicin with improved efficacy compared to the single components against murine cutaneous leishmaniasis. A formulation of compound containing 15% paromomycin and 0.5% gentamicin was evaluated in a phase II clinical trial in patients with cutaneous *Leishmania panamensis*; the cure rates for patients treated with compound and placebo were 61 and 55%, respectively; the mean cure times were 35 days for the drug-treated group and 56 days for the placebo group. No local or systemic side effects were observed.

SOURCE – Walter Reed Army Institute, Washington, DC (US).

REFERENCES

1. Grogl, M. et al. (Department of the Army) *Antileishmanial compsn. for topical application*. WO 9406439.

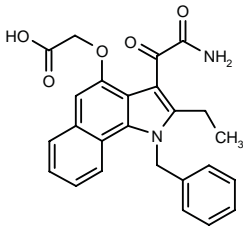
2. Grogl, M. et al. *Successful topical treatment of murine cutaneous leishmaniasis with a combination of paromomycin (Aminosidine) and gentamicin*. J Parasitol 1999, 85(2): 354.

3. Soto, J.M. et al. *Treatment of cutaneous leishmaniasis with a topical antileishmanial drug (WR279396): Phase 2 pilot study*. Am J Trop Med Hyg 2002, 66(2): 147.

TREATMENT OF SEPTIC SHOCK

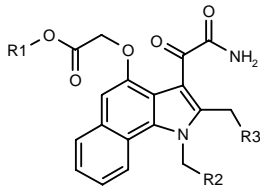
324597

2-(1-Benzyl-2-ethyl-3-oxamoyl-1 H-benzo[g]indol-4-yloxy)acetic acid



C25 H22 N2 O5; Mol wt: 430.4578

ACTION – Inhibitor of nonpancreatic secretory phospholipase A₂ (sPLA₂; IC₅₀ = 0.010 μM), potentially useful for the treatment of inflammatory diseases including sepsis, inflammatory bowel disease, adult respiratory distress syndrome, pancreatitis, asthma, allergic rhinitis, arthritis, cystic fibrosis, stroke, bronchitis, gout, etc. Other exemplified compounds are:



Compound	R1	R2	R3	Formula
324598	Me	Ph	Me	C ₂₆ H ₂₄ N ₂ O ₅
324599	Me	cyclohexyl	H	C ₂₅ H ₂₈ N ₂ O ₅
324600	H	cyclohexyl	H	C ₂₄ H ₂₆ N ₂ O ₅
324601	Me	3-(4-F-Ph)-Ph	H	C ₃₁ H ₂₅ FN ₂ O ₅
324603	H	3-(4-F-Ph)-Ph	H	C ₃₀ H ₂₃ FN ₂ O ₅

SOURCE – Lilly.

REFERENCES

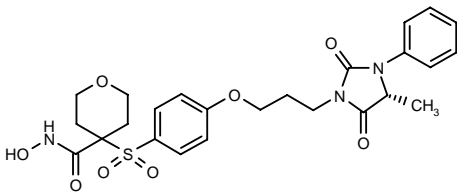
1. Bight, D.W. et al. (Eli Lilly and Company) *Novel sPLA2 inhibitors*. WO 0257231.

TREATMENT OF MUSCULOSKELETAL AND CONNECTIVE TISSUE DISEASES

ANTIARTHRITIC DRUGS

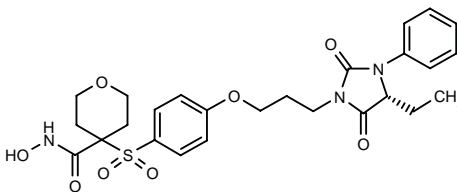
324003

4-[4-[3-[4(R)-Methyl-2,5-dioxo-3-phenylimidazolidin-1-yl]-propoxy]phenylsulfonyl]tetrahydro-2 H-pyran-4-carboxylic acid



C25 H29 N3 O8 S; Mol wt: 531.5831

ACTION – Potent collagenase 3 (MMP-13) inhibitor (IC₅₀ = 2.0 nM) with high selectivity over gelatinase A (MMP-2), neutrophil collagenase (MMP-8), gelatinase B (MMP-9) and interstitial collagenase (MMP-1) (IC₅₀ = 817, 1414, 9438 and > 10,000 nM, respectively). Potentially useful for the treatment of arthritis. Another related compound is:



324004: C26 H31 N3 O8 S

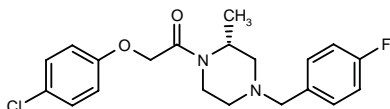
SOURCE – Pharmacia.

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1. Villamil, C. et al. *Design and synthesis of potent and selective 4,4-disubstituted α -sulphones hydroxamates as MMP inhibitors*. 224th ACS Natl Meet (Aug 18-22, Boston) 2002, Abst MEDI 309.

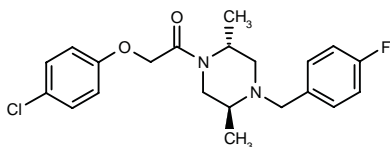
324011

2-(4-Chlorophenoxy)-1-[4-(4-fluorobenzyl)-2(*R*)-methylpiperazin-1-yl]ethanone



C20 H22 Cl F N2 O2; Mol wt: 376.8568

ACTION – Chemokine CCR1 antagonist with nanomolar affinity for CCR1 receptors ($K_i = 6$ nM) and > 1,600-fold selectivity over other G-protein-coupled receptors. The compound exhibited a favorable pharmacokinetic profile in conscious dogs, with an oral bioavailability of 100%. Potentially useful for the treatment of chronic inflammatory diseases such as multiple sclerosis and rheumatoid arthritis. Another related compound is:



324012: C21 H24 Cl F N2 O2

SOURCE – Berlex.

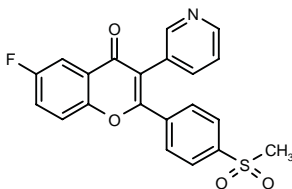
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1. Bauman, J.G. et al. (Schering AG) *Piperazine derivs. and their use as anti-inflammatory agents*. JP 2002503239, US 6207665, WO 9856771.

2. Islam, I. et al. *Synthesis and SAR of CCR1-specific non-peptide antagonists*. 224th ACS Natl Meet (Aug 18-22, Boston) 2002, Abst MEDI-334.

324050

6-Fluoro-2-[4-(methylsulfonyl)phenyl]-3-(3-pyridyl)-4*H*-1-benzopyran-4-one



C21 H14 F N O4 S; Mol wt: 395.4086

ACTION – Potent and selective cyclooxygenase type 2 (COX-2) inhibitor ($IC_{50} = 0.5$ μ g/ml in a PGE_2 assay in mouse peritoneal macrophages) with low activity against COX-1 (12% inhibition at 10 μ g/ml) and antiinflammatory activity in both carrageenan-induced paw edema and adjuvant-induced arthritis models in rats at a dose of 3 mg/kg p.o. Potentially useful for the treatment of arthritis.

SOURCE – Pacific Corp.

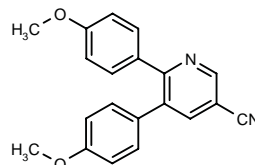
REFERENCES

1. Joo, Y.H. et al. (Pacific Corp.) *Diarylbenzopyran derivs. as cyclooxygenase-2 inhibitors*. EP 1105384, JP 2002523410, US 6340694, WO 0010993.

2. Joo, Y.H. et al. *Diarylbenzopyran derivatives as a selective inhibitor of cyclooxygenase-2*. 224th ACS Natl Meet (Aug 18-22, Boston) 2002, Abst MEDI 313.

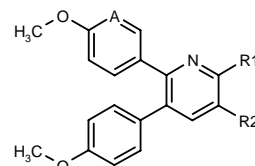
324364

5,6-Bis(4-methoxyphenyl)pyridine-3-carbonitrile



C20 H16 N2 O2; Mol wt: 316.3584

ACTION – Cyclooxygenase (COX) inhibitor, particularly active against COX-1, giving IC_{50} values of 0.017 and 1.9 μ M, respectively, against COX-1 and COX-2 in whole blood. In a rat model of adjuvant-induced arthritis, compound was shown to display analgesic activity at a dose of 3.2 mg/kg. It also inhibited acetic acid-induced stretching by 48% following oral administration to mice at a dose of 10 mg/kg. No gastric ulcerogenic activity was seen in rats given oral doses of up to 100 mg/kg. Potentially useful for the treatment of inflammatory conditions, pain, collagen diseases, immune and autoimmune diseases, thrombosis, cancer and neurodegenerative disorders. Other exemplified pyridine derivatives are:



Compound	R1	R2	A	Formula
324365	Cl	CN	CH	C ₂₀ H ₁₅ ClN ₂ O ₂
324366	OMe	CN	CH	C ₂₁ H ₁₈ N ₂ O ₃
324368	H	Me	CH	C ₂₀ H ₁₉ NO ₂
324369	H	CN	N	C ₁₉ H ₁₅ N ₃ O ₂

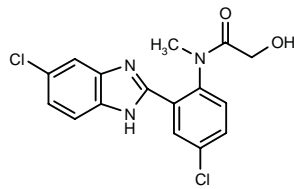
SOURCE – Fujisawa.

REFERENCES

1. Ishida, J. et al. (Fujisawa Pharmaceutical Co., Ltd.) *Pyridine derivs. useful as cyclooxygenase inhibitor*. WO 0255502.

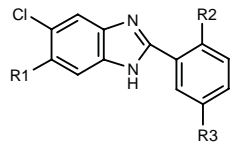
324421

N-[4-Chloro-2-(5-chloro-1*H*-benzimidazol-2-yl)phenyl]-2-hydroxy-*N*-methylacetamide



C16 H13 Cl2 N3 O2; Mol wt: 350.2037

ACTION – Osteoclast induction and differentiation inhibitor for the treatment of rheumatism and bone regeneration. The compound inhibited osteoclast differentiation and induction in tissue from mice with collagen + adjuvant-induced arthritis (72% at 0.1 μM). *In vivo*, it was shown to prevent the development of collagen-induced arthritis by 65% following oral administration to mice at 50 mg/kg/day for 50 days, while causing no severe side effects. Other exemplified heterocyclic compounds are:



Compound	R1	R2	R3	Formula
324422	H	N(Me)Ac	Cl	C ₁₆ H ₁₃ Cl ₂ N ₃ O
324423	Cl	N(Me)COCH ₂ NH ₂	H	C ₁₆ H ₁₄ Cl ₂ N ₄ O
324424	H	2-pyrrolidinyl-CON(Me)	Cl	C ₁₉ H ₁₈ Cl ₂ N ₄ O
324426	H	4-(PhCH ₂ O)-2(S)-pyrrolidinyl-CON(Me)	Cl	C ₂₆ H ₂₄ Cl ₂ N ₄ O ₂
324427	H	2-oxo-1-pyrrolidinyl	Cl	C ₁₇ H ₁₃ Cl ₂ N ₃ O
324428	H	1-pyrrolidinyl	Cl	C ₁₇ H ₁₅ Cl ₂ N ₃

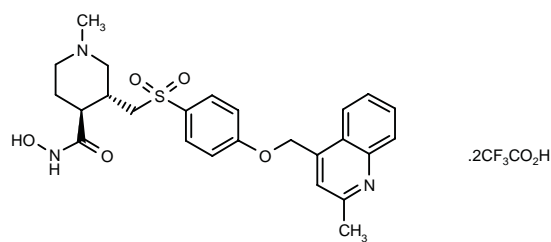
SOURCE – Sumitomo Pharmaceuticals.

REFERENCES

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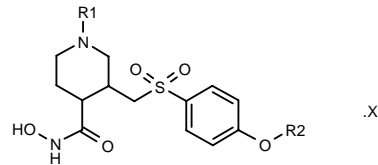
324451

1-Methyl-3(*R*)-[4-(2-methylquinolin-4-ylmethoxy)phenyl-sulfonylmethyl]piperidine-4(*S*)-carbohydroxamic acid bis-(trifluoroacetate)

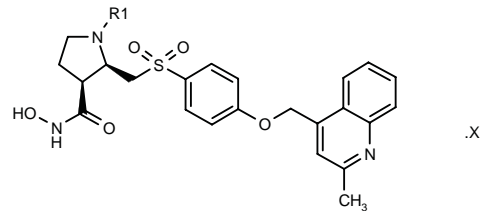


C25 H29 N3 O5 S . 2 C2 H F3 O2; Mol wt: 711.6299

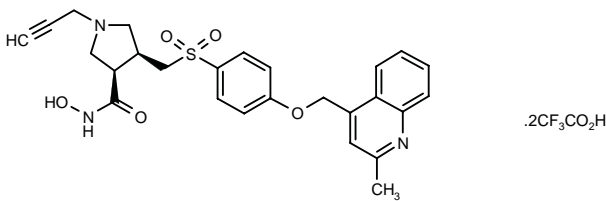
ACTION – Matrix metalloproteinase (MMP) and TNF-α inhibitor, potentially useful for the treatment of a broad range of inflammatory and thromboembolic disorders including rheumatoid arthritis, osteoarthritis, acute infection, age-related macular degeneration, alcohol abuse, allergy, asthma, anorexia, aneurysm, atherosclerosis, atopic dermatitis, autoimmune disorders, cachexia, chronic fatigue syndrome, chronic obstructive pulmonary disease, congestive heart failure, Crohn's disease, HIV infection, multiple sclerosis, arthritis, etc. Other specifically claimed compounds include the following:



Compound	R1	R2	X	Isomer	Formula
324452	Me	2-Me-4-quinolinyl-CH ₂	2CF ₃ CO ₂ H	3S,4S	C ₂₆ H ₂₉ N ₃ O ₅ S. 2C ₂ HF ₃ O ₂
324453	ethynyl-CH ₂	2-Me-4-quinolinyl-CH ₂	2CF ₃ CO ₂ H	3S,4S	C ₂₇ H ₂₉ N ₃ O ₅ S. 2C ₂ HF ₃ O ₂
324454	i-Pr	2-Me-4-quinolinyl-CH ₂	2CF ₃ CO ₂ H	3R,4R	C ₂₇ H ₃₃ N ₃ O ₅ S. 2C ₂ HF ₃ O ₂
324457	H	3-Me-Ph	CF ₃ CO ₂ H	3S,4S	C ₂₀ H ₂₄ N ₂ O ₅ S. C ₂ HF ₃ O ₂



Compound	R1	X	Formula
324455	H	2CF ₃ CO ₂ H	C ₂₃ H ₂₅ N ₃ O ₅ S.2C ₂ HF ₃ O ₂
324458	SO ₂ Me	CF ₃ CO ₂ H	C ₂₄ H ₂₇ N ₃ O ₇ S ₂ .C ₂ HF ₃ O ₂
324459	Ac	CF ₃ CO ₂ H	C ₂₅ H ₂₇ N ₃ O ₆ S.C ₂ HF ₃ O ₂



324456: C26 H27 N3 O5 S . 2 C2 H F3 O2

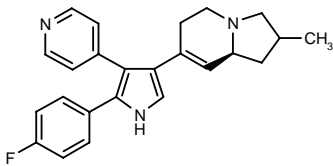
SOURCE – Bristol-Myers Squibb.

REFERENCES

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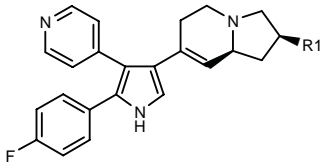
324592

(8a*S*)-7-[5-(4-Fluorophenyl)-4-(4-pyridyl)-1*H*-pyrrol-3-yl]-2-methyl-1,2,3,5,6,8a-hexahydroindolizine

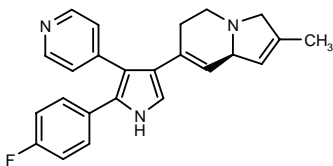


C24 H24 F N3; Mol wt: 373.4726

ACTION – Agent with the ability to inhibit the production of inflammatory cytokines, particularly IL-1β and TNF-α, as demonstrated in human peripheral blood cells by respective IC₅₀ values of 0.0017 and 0.0022 μM. *In vivo*, it prevented the lipopolysaccharide-stimulated production of TNF-α in mice with an oral ED₅₀ of 0.71 mg/kg, and it displayed an oral ID₅₀ of 1.2 mg/kg in a rat model of adjuvant-induced arthritis. Potentially useful for the treatment of disorders associated with inflammation, bone resorption, pain and pyrexia including rheumatoid arthritis, osteoarthritis, viral infection, cancer and hepatitis, and also allergic diseases, septicemia, psoriasis, asthma, degenerative arthritis, Crohn’s disease, systemic lupus erythematosus, osteoporosis, ulcerative colitis, diabetes, nephritis, ischemic heart disease, Alzheimer’s disease and arteriosclerosis. Other exemplified pyrrole derivatives include the following:



Compound	R1	Formula
324593	Ph	C ₂₉ H ₂₆ FN ₃
324595	Et	C ₂₅ H ₂₆ FN ₃
324596	Pr	C ₂₆ H ₂₈ FN ₃



324594: C24 H22 F N3

SOURCE – Sankyo.

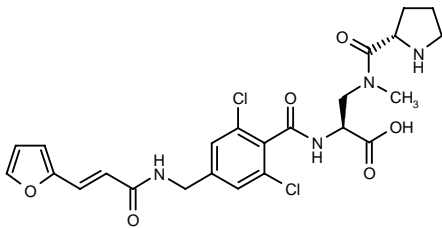
REFERENCES

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324967

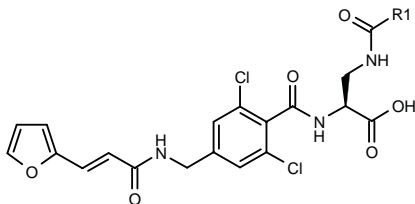
2(*S*)-[2,6-Dichloro-4-[3-(2-furyl)-2-propenamidoethyl]-benzamido]-3-[*N*-methyl-*N*-[pyrrolidin-2(*S*)-ylcarbonyl]-amino]propionic acid

N-[2,6-Dichloro-4-[3-(2-furyl)-2-propenamidoethyl]-benzoyl]-3-[*N*-methyl-*N*-(*L*-prolyl)amino]-*L*-alanine

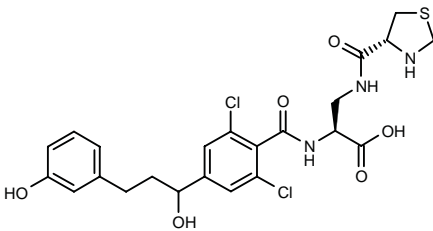


C24 H26 Cl2 N4 O6; Mol wt: 537.3974

ACTION – Inhibitor of the interaction of LFA-1 with cell adhesion molecules, proven to inhibit the binding of LFA-1 to ICAM-1 with an IC₅₀ of 0.009 μM; it exhibited low plasma protein binding. Potentially useful for the treatment of inflammatory disorders such as arthritis, psoriasis, transplant rejection, asthma and inflammatory bowel disease. Other exemplified compounds are:



Compound	R2	Formula
324969	4(<i>S</i>)-OH-2(<i>R</i>)-pyrrolidinyl	C ₂₃ H ₂₄ Cl ₂ N ₄ O ₇
324971	2-oxo-4(<i>R</i>)-thiazolidinyl	C ₂₂ H ₂₀ Cl ₂ N ₄ O ₇ S
324973	2(<i>S</i>)-Pip	C ₂₄ H ₂₆ Cl ₂ N ₄ O ₆
324974	2-THF	C ₂₃ H ₂₃ Cl ₂ N ₃ O ₇



324970: C23 H25 Cl2 N3 O6 S

SOURCE – Genentech.

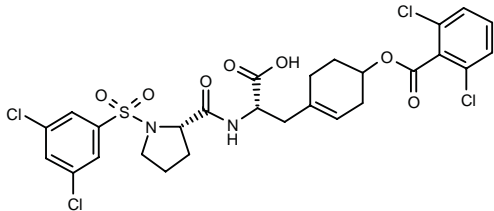
REFERENCES

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325066

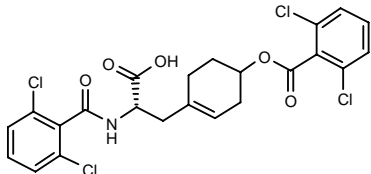
1-(3,5-Dichlorophenylsulfonyl)-L-prolyl-3-[4-(2,6-dichlorobenzoyloxy)-1-cyclohexen-1-yl]-L-alanine

3-[4-(2,6-Dichlorobenzoyloxy)-1-cyclohexen-1-yl]-2(S)-[1-(3,5-dichlorophenylsulfonyl)pyrrolidin-2(S)-ylcarbox-amido]propionic acid



C27 H26 Cl4 N2 O7 S; Mol wt: 664.3874

ACTION – $\alpha_4\beta_1$ (VLA-4) integrin receptor antagonist that inhibited the adhesion of VCAM-1-transfected CHO cells to VLA-4-transfected HL-60 cells with an IC_{50} of < 0.02 μ M. Potentially useful for the treatment of autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus and multiple sclerosis, allergic disorders including asthma, atopic dermatitis and rhinitis, and also inflammatory bowel disease, nephritis, hepatitis, CNS inflammatory disorders, arteriosclerosis, diabetes, cancer, etc. Another exemplified cyclohexane derivative is:



325067: C23 H19 Cl4 N O5

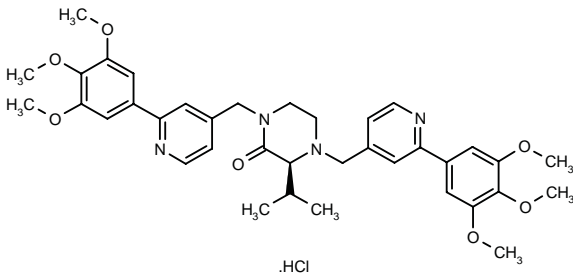
SOURCE – Kaken.

REFERENCES

1. Shimano, M. et al. (Kaken Pharmaceutical Co., Ltd.) *Cyclohexane derivs.* JP 2002201168.

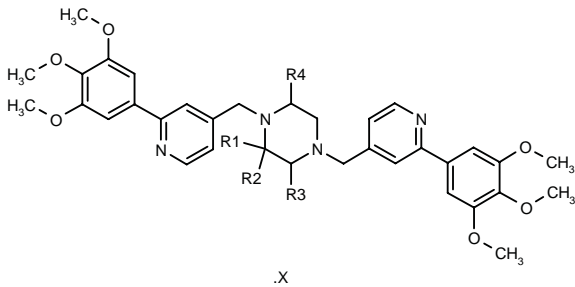
325086

1,4-Bis[2-(3,4,5-trimethoxyphenyl)pyridin-4-ylmethyl]-3(S)-isopropylpiperazin-2-one hydrochloride



C37 H44 N4 O7 . HCl; Mol wt: 693.2365

ACTION – Cell adhesion and/or cell infiltration inhibitor with potential in the treatment of allergy, asthma, inflammation, rheumatism and arteriosclerosis. Compound inhibited the TNF- α -stimulated adhesion of U-937 cells to human umbilical vein endothelial cell (HUVEC)-coated plates by 63 and 77%, respectively, at 1 and 10 μ M. Other exemplified piperazine derivatives are:



Compound	R1	R2	R3	R4	Isomer	X	Formula
325087	H	Me	H	Me	cis	4HCl	C ₃₆ H ₄₄ N ₄ O ₆ ·4HCl
325088	H	H	Me	Me	trans	4HCl	C ₃₆ H ₄₄ N ₄ O ₆ ·4HCl
325089	H	H	CH2OH	H		dimaleate	C ₃₅ H ₄₂ N ₄ O ₇ ·2C ₄ H ₄ O ₄
325090	-O-		H	H		HCl	C ₃₄ H ₃₈ N ₄ O ₇ ·HCl
325091	-O-		Me	H	3S	HCl	C ₃₅ H ₄₀ N ₄ O ₇ ·HCl
325092	-O-	i-Pr		H	3R	3HCl	C ₃₇ H ₄₄ N ₄ O ₇ ·3HCl
325093	-O-	i-Bu		H	3S	HCl	C ₃₈ H ₄₆ N ₄ O ₇ ·HCl
325094	-O-		CH2Ph	H	3S	HCl	C ₄₁ H ₄₄ N ₄ O ₇ ·HCl

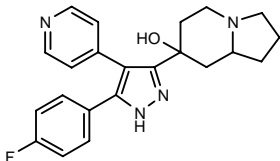
SOURCE – Kowa.

REFERENCES

1. Kodama, T. et al. (Kowa Co., Ltd.) *Piperazine deriv.* US 6432957.

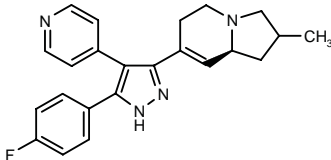
325169

(\pm)-7-[5-(4-Fluorophenyl)-4-(4-pyridyl)-1H-pyrazol-3-yl]-perhydroindolizin-7-ol



C22 H23 F N4 O; Mol wt: 378.4487

ACTION – Agent with the ability to inhibit the production of inflammatory cytokines, particularly IL-1 β and TNF- α . It inhibited the lipopolysaccharide-stimulated production of TNF- α and IL-1 β in human peripheral blood cells with respective IC_{50} values of 0.070 and 0.035 μ M. Potentially useful as an analgesic and antiinflammatory agent for use in the treatment of chronic rheumatoid arthritis, osteoarthritis, allergic disorders, sepsis, psoriasis, osteoporosis, ulcerative colitis, diabetes, hepatitis and arteriosclerosis. Another exemplified compound is:



325170: C23 H23 F N4

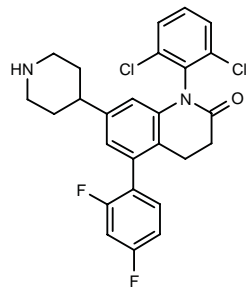
SOURCE – Sankyo.

REFERENCES

1. Kimura, T. et al. (Sankyo Co., Ltd.) *Cpds. substd. with bicyclic amino groups.* WO 0257265.

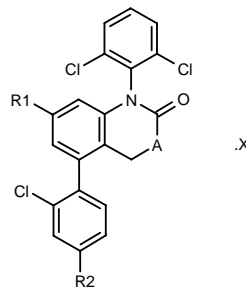
325185

1-(2,6-Dichlorophenyl)-5-(2,4-difluorophenyl)-7-(4-piperidin-1,2,3,4-tetrahydroquinolin-2-one

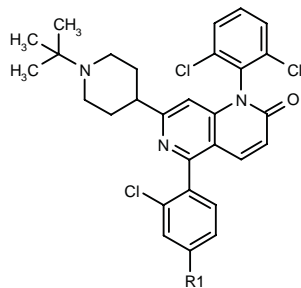


C26 H22 Cl2 F2 N2 O; Mol wt: 487.3748

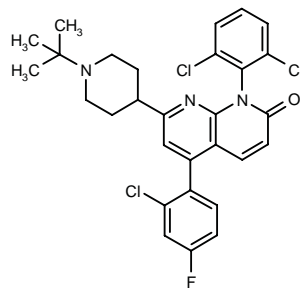
ACTION – Agent with p38 kinase-inhibitory activity, potentially useful for the treatment of inflammatory conditions including arthritis, osteoporosis and Crohn's disease. Other exemplified compounds include the following:



Compound	R1	R2	A	X	Formula
325186	4-(4-Pyr-CH2)-1-Piz-CH2	H	NH		C ₃₁ H ₂₈ Cl ₃ N ₅ O
325187	1-(OHCH2CH2)-4-Pip-CH2	F	NH		C ₂₈ H ₂₇ Cl ₃ FN ₃ O ₂
325188	2-Me-1-Piz-CH2	H	NH		C ₂₆ H ₂₅ Cl ₃ N ₄ O
325192	4-i-Pr-1-Piz-CO	H	O		C ₂₈ H ₂₆ Cl ₃ N ₃ O ₃
325196	8-azabicyclo-[3.2.1]octan-3-yl	F	CH2	CF3CO2H	C ₂₈ H ₂₄ Cl ₃ FN ₂ O. C ₂ HF ₃ O ₂



Compound	R1	Formula
325190	H	C ₂₉ H ₂₈ Cl ₃ N ₃ O
325191	F	C ₂₉ H ₂₇ Cl ₃ FN ₃ O



325189: C29 H27 Cl3 F N3 O

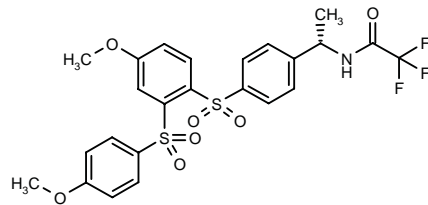
SOURCE – Merck & Co.

REFERENCES

1. Doherty, J.B. et al. (Merck & Co., Inc.) (Halo-benzo carbonyl)heterocyclic fused phenyl p38 kinase inhibiting agents. WO 0258695.

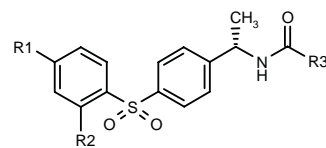
325613

2,2,2-Trifluoro-N-[1(S)-[4-[4-methoxy-2-(4-methoxy-phenylsulfonyl)phenylsulfonyl]phenyl]ethyl]acetamide

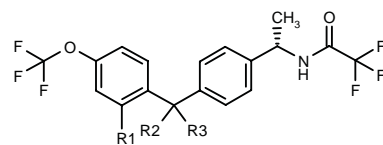


C24 H22 F3 N O7 S2; Mol wt: 557.5638

ACTION – Agent with the ability to activate cannabinoid CB₂ receptors, potentially useful for the treatment of inflammatory and immunomodulatory diseases and respiratory disorders, in particular rheumatoid arthritis, multiple sclerosis, psoriasis, seasonal allergic rhinitis and chronic obstructive pulmonary disease. Other exemplified compounds include the following:



Compound	R1	R2	R3	Formula
325618	Cl	2-F-PhSO2	CF3	C ₂₂ H ₁₆ ClF ₄ NO ₅ S ₂
325619	OMe	2-F-PhSO2	Me	C ₂₃ H ₂₂ FNO ₆ S ₂
325621	OCHF2	2-F-PhSO2	CF3	C ₂₃ H ₁₇ F ₆ NO ₆ S ₂
325622	Cl	2-F-PhCO	CF3	C ₂₃ H ₁₆ ClF ₄ NO ₄ S
325623	Cl	4-Cl-PhO	CF3	C ₂₂ H ₁₆ Cl ₂ F ₃ NO ₄ S
325626	OMe	4-Cl-PhSO2	CF3	C ₂₃ H ₁₉ ClF ₃ NO ₆ S ₂



Compound	R1	R2	R3	Formula
325624	2-F-PhSO2	H	H	C ₂₄ H ₁₈ F ₇ NO ₄ S
325625	2-F-PhS	-O-		C ₂₄ H ₁₆ F ₇ NO ₃ S

SOURCE – Schering-Plough.

REFERENCES

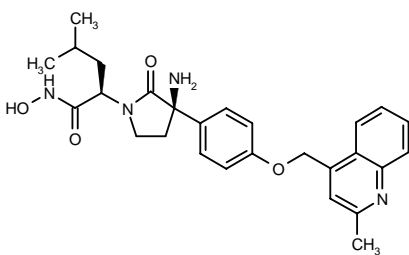
1. Kozlowski, J.A. et al. (Schering Corp.) *Cannabinoid receptor ligands*. WO 0262750.

BMS-561392²⁻⁵

320954

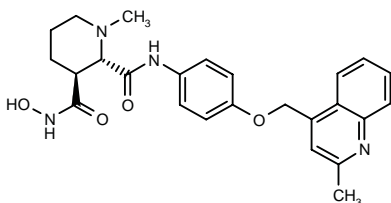
2(*R*)-[3(*R*)-Amino-3-[4-(2-methylquinolin-4-ylmethoxy)-phenyl]-2-oxopyrrolidin-1-yl]-4-methylpentanehydroxamic acid

DPC-333



C27 H32 N4 O4; Mol wt: 476.5738

ACTION – Potent and selective inhibitor of TNF- α -converting enzyme (TACE) with good oral bioavailability in rats and dogs and active in suppressing TNF- α production induced by lipopolysaccharide in mice (ED_{50} = 6 mg/kg p.o.). It also prevented joint destruction in a mouse model of collagen-induced arthritis. Currently in advanced phase II clinical trials in rheumatoid arthritis patients. Another related compound is:



323897^{1,4}: C25 H28 N4 O4

SOURCE – Bristol-Myers Squibb.

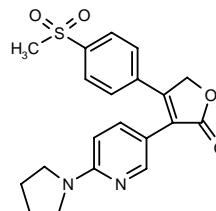
REFERENCES

1. Xue, C.-B. et al. (DuPont Pharmaceuticals Co.) *Cyclic hydroxamic acids as metalloproteinase inhibitors*. EP 1087937, US 6429213, WO 9965867.
2. Benedek, I.H. et al. *Evaluation of safety, tolerability and pharmacokinetics of single escalating oral doses of DPC 333 in healthy volunteers*. Clin Pharmacol Ther 2002, 71(2): Abst TP11-75.
3. Decicco, C.P. *Rational design and therapeutic application of metalloproteinase inhibitors of TNF-alpha*. 221st ACS Natl Meet (April 1-5, San Diego) 2001, Abst MEDI 189.
4. Duan, J.J.-W. et al. *Discovery of selective and orally bioavailable TACE inhibitors*. 224th ACS Natl Meet (Aug 18-22, Boston) 2002, Abst MEDI 426.
5. Vaddi, K.G. et al. *Characterization of the anti-inflammatory effects of a selective TACE inhibitor DPC 333*. Arthritis Rheum 2001, 44(9, Suppl.): S368.

UR-8962*

312635

4-[4-(Methylsulfonyl)phenyl]-3-[6-(1-pyrrolidinyl)pyridin-3-yl]furan-2(5*H*)-one



C20 H20 N2 O4 S; Mol wt: 384.4540

ACTION – Potent and selective cyclooxygenase type 2 (COX-2) inhibitor that completely inhibited COX-2 activity in a whole-cell assay (at 1 μ M) and in human whole blood (at 10 μ M). In rat models, compound at doses of 1-10 mg/kg showed good antiinflammatory and analgesic efficacy, with comparable activity to celecoxib and rofecoxib. Further investigations predicted good absorption and metabolic stability in humans. Selected for further preclinical development.

SOURCE – Uriach.

REFERENCES

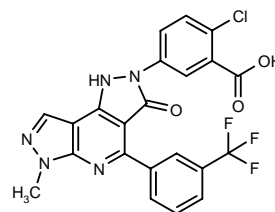
1. Almansa Rosales, C. et al. (J. Uriach & Cía., SA) *Novel heterocyclic cpds. with anti-inflammatory activity*. WO 0183475.
2. Almansa, C. et al. *Synthesis and SAR of 4-pyrrolidinylheterocycles as COX-2 selective inhibitors*. Drugs Fut 2002, 27(Suppl. A): Abst P108.

*Identified compound **312635** (see **312616**) Drug Data Rep 2002, 024(02): 0172.

IMMUNOMODULATING AGENTS

323762

2-Chloro-5-[6-methyl-3-oxo-4-[3-(trifluoromethyl)phenyl]-1,2,3,6-tetrahydropyrazolo[3,4-*b*:3',4'-*d*]pyridin-2-yl]-benzoic acid



C22 H13 Cl F3 N5 O3; Mol wt: 487.8237

ACTION – Small-molecule inhibitor of the interaction between CD28 and the human costimulatory molecule B7.1 (CD80; IC_{50} = 7 nM) potentially useful for the treatment of transplant rejection and autoimmune diseases. Other related compounds are:

SOURCE – Schering-Plough.

REFERENCES

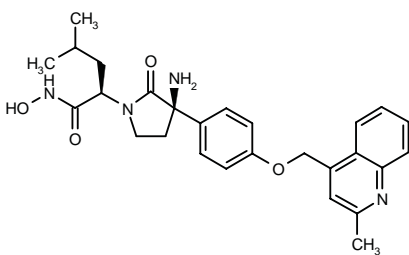
1. Kozlowski, J.A. et al. (Schering Corp.) *Cannabinoid receptor ligands*. WO 0262750.

BMS-561392²⁻⁵

320954

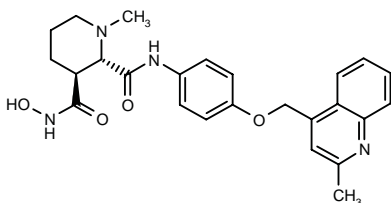
2(*R*)-[3(*R*)-Amino-3-[4-(2-methylquinolin-4-ylmethoxy)-phenyl]-2-oxopyrrolidin-1-yl]-4-methylpentanehydroxamic acid

DPC-333



C27 H32 N4 O4; Mol wt: 476.5738

ACTION – Potent and selective inhibitor of TNF- α -converting enzyme (TACE) with good oral bioavailability in rats and dogs and active in suppressing TNF- α production induced by lipopolysaccharide in mice (ED_{50} = 6 mg/kg p.o.). It also prevented joint destruction in a mouse model of collagen-induced arthritis. Currently in advanced phase II clinical trials in rheumatoid arthritis patients. Another related compound is:



323897^{1,4}: C25 H28 N4 O4

SOURCE – Bristol-Myers Squibb.

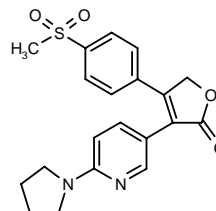
REFERENCES

1. Xue, C.-B. et al. (DuPont Pharmaceuticals Co.) *Cyclic hydroxamic acids as metalloproteinase inhibitors*. EP 1087937, US 6429213, WO 9965867.
2. Benedek, I.H. et al. *Evaluation of safety, tolerability and pharmacokinetics of single escalating oral doses of DPC 333 in healthy volunteers*. Clin Pharmacol Ther 2002, 71(2): Abst TP11-75.
3. Decicco, C.P. *Rational design and therapeutic application of metalloproteinase inhibitors of TNF-alpha*. 221st ACS Natl Meet (April 1-5, San Diego) 2001, Abst MEDI 189.
4. Duan, J.J.-W. et al. *Discovery of selective and orally bioavailable TACE inhibitors*. 224th ACS Natl Meet (Aug 18-22, Boston) 2002, Abst MEDI 426.
5. Vaddi, K.G. et al. *Characterization of the anti-inflammatory effects of a selective TACE inhibitor DPC 333*. Arthritis Rheum 2001, 44(9, Suppl.): S368.

UR-8962*

312635

4-[4-(Methylsulfonyl)phenyl]-3-[6-(1-pyrrolidinyl)pyridin-3-yl]furan-2(5*H*)-one



C20 H20 N2 O4 S; Mol wt: 384.4540

ACTION – Potent and selective cyclooxygenase type 2 (COX-2) inhibitor that completely inhibited COX-2 activity in a whole-cell assay (at 1 μ M) and in human whole blood (at 10 μ M). In rat models, compound at doses of 1-10 mg/kg showed good antiinflammatory and analgesic efficacy, with comparable activity to celecoxib and rofecoxib. Further investigations predicted good absorption and metabolic stability in humans. Selected for further preclinical development.

SOURCE – Uriach.

REFERENCES

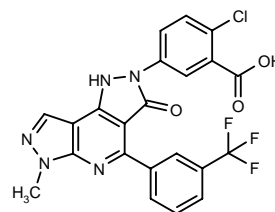
1. Almansa Rosales, C. et al. (J. Uriach & Cía., SA) *Novel heterocyclic cpds. with anti-inflammatory activity*. WO 0183475.
2. Almansa, C. et al. *Synthesis and SAR of 4-pyrrolidinylheterocycles as COX-2 selective inhibitors*. Drugs Fut 2002, 27(Suppl. A): Abst P108.

*Identified compound **312635** (see **312616**) Drug Data Rep 2002, 024(02): 0172.

IMMUNOMODULATING AGENTS

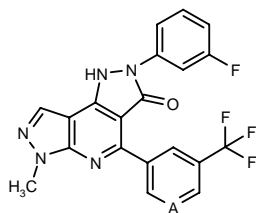
323762

2-Chloro-5-[6-methyl-3-oxo-4-[3-(trifluoromethyl)phenyl]-1,2,3,6-tetrahydropyrazolo[3,4-*b*:3',4'-*d*]pyridin-2-yl]-benzoic acid



C22 H13 Cl F3 N5 O3; Mol wt: 487.8237

ACTION – Small-molecule inhibitor of the interaction between CD28 and the human costimulatory molecule B7.1 (CD80; IC_{50} = 7 nM) potentially useful for the treatment of transplant rejection and autoimmune diseases. Other related compounds are:



Compound	A	Formula
323760	CH	C ₂₁ H ₁₃ F ₄ N ₅ O
323761	N	C ₂₀ H ₁₂ F ₄ N ₆ O

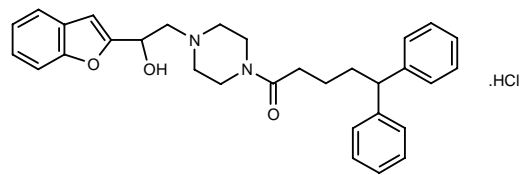
SOURCE – Wyeth.

REFERENCES

1. Green, N. et al. *Structure-activity studies of a series of dipyrzolo [3,4-b:3',4'-d]-pyridin-3-ones binding to the immune regulatory protein B7-1.* 224th ACS Natl Meet (Aug 18-22, Boston) 2002, Abst MEDI 11.

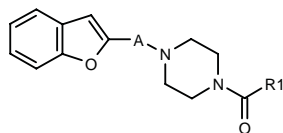
324281

1-[4-[2-(Benzofuran-2-yl)-2-hydroxyethyl]piperazin-1-yl]-5,5-diphenyl-1-pentanone hydrochloride



C31 H34 N2 O3 . HCl; Mol wt: 519.0815

ACTION – Immunomodulating agent that inhibits the phosphorylation of STAT6, potentially useful for the treatment of allergic diseases. Other exemplified benzo-furan derivatives are:



Compound	R1	A	Formula
324282	CH=CHPh	-CH(OH)CH2-	C ₂₃ H ₂₄ N ₂ O ₃
324283	CH2CH(Ph)2	-CH(OH)CH2-	C ₂₉ H ₃₀ N ₂ O ₃
324284	CH2CH(Ph)2	-CO-	C ₂₈ H ₂₆ N ₂ O ₃
324285	CH2CH(Ph)2	-CH2CH(OH)-	C ₂₉ H ₃₀ N ₂ O ₃
324286	CH2CH(Ph)2	-CH2-	C ₂₈ H ₂₈ N ₂ O ₂
324287	CH2CH(Ph)2	-(CH2)2-	C ₂₉ H ₃₀ N ₂ O ₂

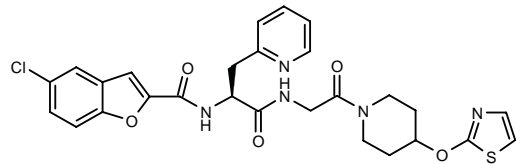
SOURCE – Pola Chemical.

REFERENCES

1. Kawakatsu, N. et al. (Pola Chemical Industries Inc.) *Benzofuran derivs. and pharmaceutical compsns. containing the same.* WO 0253550.

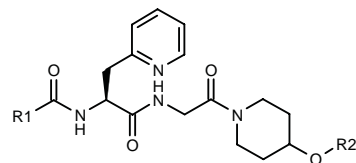
324353

5-Chloro-*N*-[1(*S*)-[*N*-[2-oxo-2-[4-(thiazol-2-yloxy)piperidin-1-yl]ethyl]carbamoyl]-2-(2-pyridyl)ethyl]-1-benzofuran-2-carboxamide



C27 H26 Cl N5 O5 S; Mol wt: 568.0514

ACTION – Nitric oxide synthase (NOS) inhibitor with potential as an immunosuppressant and in the treatment of transplant rejection. The compound completely prevented the production of NO in lipopolysaccharide- and interferon gamma-stimulated murine macrophage RAW264.7 cells at a concentration of 1 μM. Other exemplified peptide compounds are:



Compound	R1	R2	Formula
324358	4-Cl-PhCH=CH	2-pyrazinyl	C ₂₈ H ₂₈ ClN ₆ O ₄
324359	5-Cl-2-benzofuryl	6-MeO-2-Pyr	C ₃₀ H ₃₀ ClN ₅ O ₆
324360	5-Cl-2-benzofuryl	2-Pyr	C ₂₉ H ₂₈ ClN ₅ O ₅
324361	4-Cl-PhCH=CH	Ph	C ₃₀ H ₃₁ ClN ₄ O ₄
324362	5-Cl-2-benzofuryl	CH2CF3	C ₂₆ H ₂₆ ClF ₃ N ₄ O ₅
324363	4-Cl-PhCH=CH	i-Pr	C ₂₇ H ₃₃ ClN ₄ O ₄

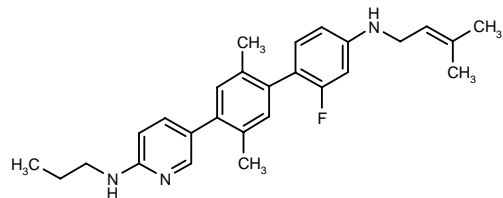
SOURCE – Fujisawa.

REFERENCES

1. Shima, I. et al. (Fujisawa Pharmaceutical Co., Ltd.) *Peptide cpds.* WO 0255541.

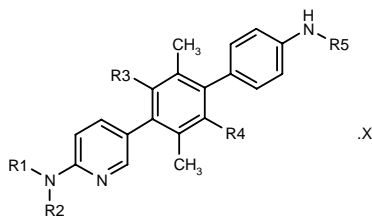
325147

5-[2'-Fluoro-2,5-dimethyl-4'-(3-methyl-2-butenylamino)-biphenyl-4-yl]-*N*-propylpyridin-2-amine

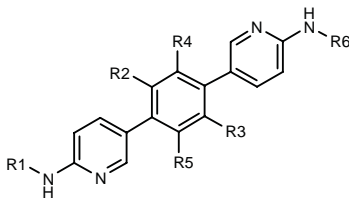


C27 H32 F N3; Mol wt: 417.5688

ACTION – Immunosuppressant shown to inhibit the production of IgE antibodies *in vivo*, as it prevented the development of passive cutaneous anaphylaxis (PCA) in ovalbumin-challenged mice at a dose of 40 mg/kg p.o. Potentially useful for the treatment of transplant rejection, ulcerative colitis, systemic lupus erythematosus, myasthenia gravis, systemic progressive scleroderma, chronic rheumatoid arthritis, glomerulonephritis, interstitial cystitis, etc. Other exemplified heterotricyclic compounds include the following:



Compound	R1	R2	R3=R4	R5	X	Formula
325149	H	i-Pr	Me	cyclo-pentyl		C ₂₉ H ₃₇ N ₃
325150	H	i-Pr	Me	Pr		C ₂₇ H ₃₅ N ₃
325152	cyclopropyl-CH ₂	COCH ₂ -OMe	OMe	COCH ₂ -OMe		C ₃₁ H ₃₇ N ₃ O ₆
325153	H	cyclo-pentyl	Me	cyclo-pentyl		C ₃₁ H ₃₉ N ₃
325155	H	CH ₂ CH=C(Me) ₂	Me	CH ₂ CH=C(Me) ₂	HCl	C ₃₁ H ₃₉ N ₃ .HCl



Compound	R1	R2=R3	R4=R5	R6	Formula
325156	i-Pr	OMe	Me	i-Pr	C ₂₆ H ₃₄ N ₄ O ₂
325157	i-Bu	Me	Me	i-Bu	C ₂₈ H ₃₈ N ₄
325158	i-Pr	F	F	i-Pr	C ₂₂ H ₂₂ F ₄ N ₄

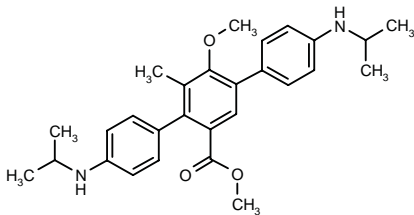
SOURCE – Shionogi.

REFERENCES

1. Tsuru, T. et al. (Shionogi & Co. Ltd.) *Hetero-tricyclic cpds. having substd. amino groups*. WO 0257237.

325159

4,4''-Bis(isopropylamino)-5'-methoxy-6'-methyl-1,1':4',1''-terphenyl-2'-carboxylic acid methyl ester



C28 H34 N2 O3; Mol wt: 446.5876

ACTION – Immunosuppressant shown to inhibit the production of IgE antibodies *in vivo*, as it prevented the development of passive cutaneous anaphylaxis (PCA) in ovalbumin-challenged mice at a dose of 40 mg/kg p.o. Potentially useful for the treatment of transplant rejection, ulcerative colitis, systemic lupus erythematosus, myasthenia gravis, systemic progressive scleroderma, chronic rheumatoid arthritis, glomerulonephritis or interstitial cystitis, among other disorders.

SOURCE – Shionogi.

REFERENCES

1. Tsuru, T. et al. (Shionogi & Co. Ltd.) *Terphenyl cpds. bearing substd. amino groups*. WO 0257216.

325454

Tetravalent meningococcal A, C, W-135 and Y polysaccharide–diphtheria toxoid conjugate vaccine

ACTION – Tetravalent vaccine composed of purified adipic acid-derivatized capsular polysaccharides from *Neisseria meningitidis* serogroups A, C, W-135 and Y, conjugated to diphtheria toxoid protein. An unadjuvanted form of the vaccine was tested in young healthy adults and children. Adults were given a single dose of the vaccine and the antibody response to each of the serogroups was analyzed at day 28 postvaccination. The vaccine elicited an immune response against the 4 serotypes and was found to be safe. In young children (12-15 months of age), the antibody response was similar to that obtained with the licensed polysaccharide vaccine (C polysaccharide without protein conjugate), but the level of bactericidal antibodies was much higher with the tetravalent conjugate. Furthermore, this vaccine elicited long-lasting protection, whereas the response induced by the licensed polysaccharide vaccine wanes after 1 year.

SOURCE – Aventis Pasteur.

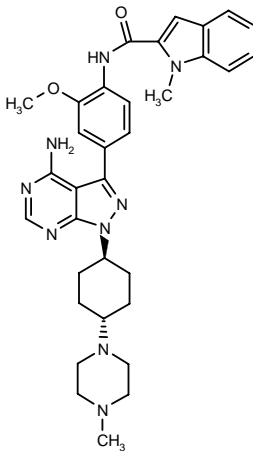
REFERENCES

1. Ryall, R.P. (Aventis Pasteur MSD) *Multivalent meningococcal polysaccharide-protein conjugate vaccine*. WO 0258737.

A-420983

324385

N-[4-[4-Amino-1-[*trans*-4-(4-methylpiperazin-1-yl)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl]-1-methyl-1*H*-indole-2-carboxamide



C33 H39 N9 O2; Mol wt: 593.7321

ACTION – Protein tyrosine kinase Lck inhibitor (IC_{50} = 37 nM) with high selectivity over a panel of protein tyrosine kinases including Fyn, KDR and Tie-2 (IC_{50} = 330, > 5000 and 1470 nM, respectively). It inhibited IL-2 production in human whole blood (IC_{50} = 11 nM) and *in vivo* (ED_{50} = 1.5 mg/kg), showed good oral bioavailability in mice, rats and dogs (30-35%) and was metabolically stable in human, rat, dog and mouse microsomes. *In vivo*, compound was active in several animal models of transplant rejection, protecting against allograft rejection following oral administration and suppressing both the acute phase and relapse of experimental autoimmune encephalomyelitis, a rodent model of multiple sclerosis. Potentially useful for the treatment of transplant rejection and autoimmune diseases.

SOURCE – Abbott.

REFERENCES

1. Hirst, G.C. et al. (BASF AG) *Pyrazolopyrimidines as therapeutic agents*. EP 1212327, WO 0119829.
2. Babineau, M. et al. *Pyrazolo[3,4-d]pyrimidines as orally active lck inhibitors*. Drugs Fut 2002, 27(Suppl. A): Abst C29.

ANTI-GPI VACCINE

324956

Malaria vaccine consisting of a synthetic Plasmodium falciparum glycosylphosphatidylinositol (GPI) glycan conjugated to activated ovalbumin or keyhole limpet hemocyanin (KLH)

ACTION – Prototype malaria vaccine, a *Plasmodium falciparum* glycosylphosphatidylinositol (GPI) glycan conjugated to activated ovalbumin or keyhole limpet hemocyanin (KLH) and able to significantly protect mice against acidosis, pulmonary edema, cerebral syndrome and mortality due to *Plasmodium berghei* infection. The anti-GPI antibodies produced by mice immunized with the vaccine also specifically neutralized *P. falciparum*-induced TNF- α production from macrophages.

SOURCES – Massachusetts Institute of Technology, Cambridge, MA (US); Walter and Eliza Hall Institute of Medical Research, Melbourne (AU).

REFERENCES

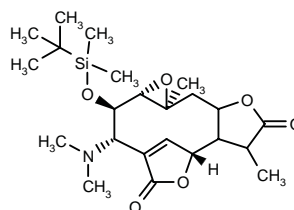
1. Schofield, L. et al. *Synthetic GPI as a candidate anti-toxic vaccine in a model of malaria*. Nature 2002, 418(6899): 785.

ONCOLYTIC DRUGS

ANTIBIOTICS AND ALKALOIDS

324318

(4*R*,8*S*,9*R*,9*aS*,10*aS*)-9-(*tert*-Butyldimethylsilyloxy)-8-(dimethylamino)-3,10a-dimethyloctahydro-4,7-methenofuro[3,2-*c*]oxireno[*f*]oxacycloundecin-2,6(3*H*)-dione



C23 H37 N O6 Si; Mol wt: 451.6323

ACTION – Mikanolide derivative with antitumor, antiviral and antibacterial activity. Compound inhibited the proliferation of human prostate cancer DU 145 and pancreatic cancer MIA PaCa-2 cells with IC_{50} values of 30 μ M. At 100 μ g/ml, it inhibited polymerase activity by $70 \pm 8\%$ in an acellular system. It also inhibited thymidine incorporation into human colon cancer HT-29 cells.

SOURCE – SCRAS.

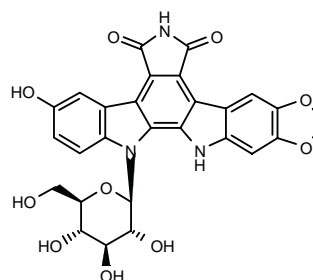
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1. Laverne, O. et al. (SCRAS [Société de Conseils de Recherches et d'Applications Scientifiques]) *Mikanolide derivs., their preparation and therapeutic uses*. FR 2819513, WO 0255523.

DNA-INTERCALATING DRUGS

322966

14-(β -D-Glucopyranosyl)-3-hydroxy-6,7,13,14-tetrahydro-5*H*-[1,3]dioxolo[4,5-*h*]indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole-5,7-dione



C27 H21 N3 O10; Mol wt: 547.4739

ACTION – Protein tyrosine kinase Lck inhibitor (IC_{50} = 37 nM) with high selectivity over a panel of protein tyrosine kinases including Fyn, KDR and Tie-2 (IC_{50} = 330, > 5000 and 1470 nM, respectively). It inhibited IL-2 production in human whole blood (IC_{50} = 11 nM) and *in vivo* (ED_{50} = 1.5 mg/kg), showed good oral bioavailability in mice, rats and dogs (30-35%) and was metabolically stable in human, rat, dog and mouse microsomes. *In vivo*, compound was active in several animal models of transplant rejection, protecting against allograft rejection following oral administration and suppressing both the acute phase and relapse of experimental autoimmune encephalomyelitis, a rodent model of multiple sclerosis. Potentially useful for the treatment of transplant rejection and autoimmune diseases.

SOURCE – Abbott.

REFERENCES

1. Hirst, G.C. et al. (BASF AG) *Pyrazolopyrimidines as therapeutic agents*. EP 1212327, WO 0119829.
2. Babineau, M. et al. *Pyrazolo[3,4-d]pyrimidines as orally active lck inhibitors*. Drugs Fut 2002, 27(Suppl. A): Abst C29.

ANTI-GPI VACCINE

324956

Malaria vaccine consisting of a synthetic Plasmodium falciparum glycosylphosphatidylinositol (GPI) glycan conjugated to activated ovalbumin or keyhole limpet hemocyanin (KLH)

ACTION – Prototype malaria vaccine, a *Plasmodium falciparum* glycosylphosphatidylinositol (GPI) glycan conjugated to activated ovalbumin or keyhole limpet hemocyanin (KLH) and able to significantly protect mice against acidosis, pulmonary edema, cerebral syndrome and mortality due to *Plasmodium berghei* infection. The anti-GPI antibodies produced by mice immunized with the vaccine also specifically neutralized *P. falciparum*-induced TNF- α production from macrophages.

SOURCES – Massachusetts Institute of Technology, Cambridge, MA (US); Walter and Eliza Hall Institute of Medical Research, Melbourne (AU).

REFERENCES

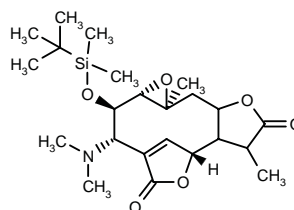
1. Schofield, L. et al. *Synthetic GPI as a candidate anti-toxic vaccine in a model of malaria*. Nature 2002, 418(6899): 785.

ONCOLYTIC DRUGS

ANTIBIOTICS AND ALKALOIDS

324318

(4*R*,8*S*,9*R*,9*aS*,10*aS*)-9-(*tert*-Butyldimethylsilyloxy)-8-(dimethylamino)-3,10a-dimethyloctahydro-4,7-methenofuro[3,2-*c*]oxireno[*f*]oxacycloundecin-2,6(3*H*)-dione



C23 H37 N O6 Si; Mol wt: 451.6323

ACTION – Mikanolide derivative with antitumor, antiviral and antibacterial activity. Compound inhibited the proliferation of human prostate cancer DU 145 and pancreatic cancer MIA PaCa-2 cells with IC_{50} values of 30 μ M. At 100 μ g/ml, it inhibited polymerase activity by $70 \pm 8\%$ in an acellular system. It also inhibited thymidine incorporation into human colon cancer HT-29 cells.

SOURCE – SCRAS.

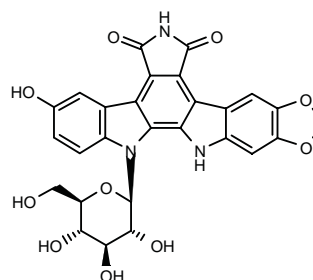
REFERENCES

1. Laverne, O. et al. (SCRAS [Société de Conseils de Recherches et d'Applications Scientifiques]) *Mikanolide derivs., their preparation and therapeutic uses*. FR 2819513, WO 0255523.

DNA-INTERCALATING DRUGS

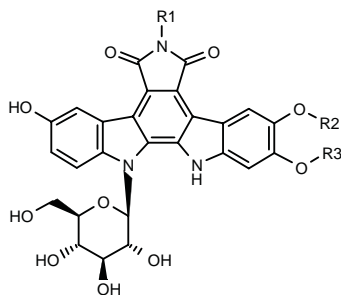
322966

14-(β -D-Glucopyranosyl)-3-hydroxy-6,7,13,14-tetrahydro-5*H*-[1,3]dioxolo[4,5-*h*]indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole-5,7-dione



C27 H21 N3 O10; Mol wt: 547.4739

ACTION – DNA topoisomerase I inhibitor (IC_{50} = 3.6 μ M against human enzyme), proven to inhibit the growth of prostate cancer DU 145 cells and ovarian cancer OVCAR-3 cells with respective IC_{50} values of 0.460 and < 0.01 μ M. Other exemplified indolocarbazole derivatives are:



Compound	R1	R2,R3	Formula
322967	CH2OH	-(CH2)2-	C ₂₉ H ₂₅ N ₃ O ₁₁
322968	CH2OH	-CH2-	C ₂₈ H ₂₃ N ₃ O ₁₁
322970	H	-(CH2)2-	C ₂₈ H ₂₃ N ₃ O ₁₀
322971	H	-C(Me)2-	C ₂₉ H ₂₅ N ₃ O ₁₀
322972	CH2OH	-C(Me)2-	C ₃₀ H ₂₇ N ₃ O ₁₁

SOURCE – Advanced Life Sciences.

REFERENCES

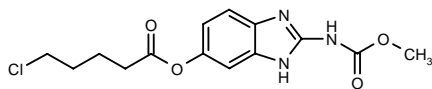
1. Zembower, D.E. et al. (Advanced Life Sciences Inc.) *Indolocarbazole anticancer agents and methods of using them*. WO 0248166.

ANTIMITOTIC DRUGS

323126

N-[6-(5-Chloropentanoyloxy)-1*H*-benzimidazol-2-yl]-carbamic acid methyl ester

5-Chloropentanoic acid 2-(methoxycarbonylamino)-1-benzimidazol-6-yl ester



C14 H16 Cl N3 O4; Mol wt: 325.7504

ACTION – Agent with potential in the treatment of cancer and viral infections, as demonstrated by its ability to inhibit the proliferation of human colon tumor HT-29 cells and murine melanoma B16 cells with IC_{50} values of 0.010 and 0.011 μ M, respectively. At 2 μ M, compound inhibited the formation of microtubules from bovine tubulin by 28%, but was inactive in a DNA binding assay. In a B16 murine melanoma model, the compound exhibited weak activity (T/C = 132%) following i.p. administration at a dose of 50 mg/kg.

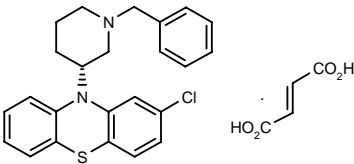
SOURCE – Procter & Gamble.

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1. Quada, J.C. Jr. et al. (The Procter & Gamble Co.) *Cpds. and method for use thereof in the treatment of cancer or viral infections*. US 6407131.

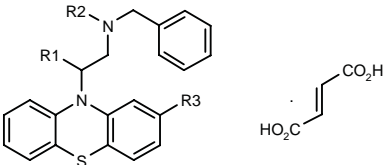
324689

10-[1-Benzylpiperidin-3(*R*)-yl]-2-chloro-10*H*-phenothiazine fumarate



C24 H23 Cl N2 S . C4 H4 O4; Mol wt: 523.0503

ACTION – Inhibitor of the mitotic kinesin KSP (K_i < 10 μ M), potentially useful for the treatment of cancer, hyperplasia, restenosis, cardiac hypertrophy, immune disorders and inflammation. Other exemplified phenothiazine derivatives include the following:



Compound	R1	R2	R3	Isomer	Formula
324690	-(CH2)3-		Cl	S	C ₂₈ H ₂₇ ClN ₂ O ₄ S
324691	-(CH2)3-		H		C ₂₈ H ₂₈ N ₂ O ₄ S
324692	H	Me	Cl		C ₂₆ H ₂₅ ClN ₂ O ₄ S
324693	H	H	Cl		C ₂₅ H ₂₃ ClN ₂ O ₄ S

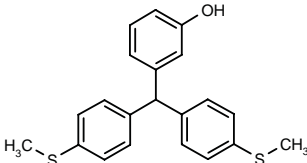
SOURCE – Cytokinetics.

REFERENCES

1. Finer, J.T. and Chabala, J.C. (Cytokinetics, Inc.) *Phenothiazine kinesin inhibitors*. WO 0257244.

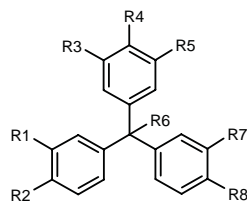
324694

3-[1,1-Bis[4-(methylsulfanyl)phenyl]methyl]phenol



C21 H20 O S2; Mol wt: 352.5200

ACTION – Inhibitor of the mitotic kinesin KSP (K_i < 100 μ M), potentially useful for the treatment of cancer, hyperplasia, restenosis, cardiac hypertrophy, immune disorders and inflammation. Other exemplified triphenylmethane derivatives include the following:



Compound	R1	R2	R3	R4	R5	R6	R7	R8	Formula
324695	H	OMe	OH	H	H	H	H	OMe	C ₂₁ H ₂₀ O ₃
324696	H	SO ₂ Me	OH	H	H	H	H	SO ₂ Me	C ₂₁ H ₂₀ O ₅ S ₂
324697	H	N(Me) ₂	OH	H	OH	H	H	N(Me) ₂	C ₂₃ H ₂₆ N ₂ O ₂
324698	N(Me) ₂	H	N(Me) ₂	H	H	H	OH	H	C ₂₃ H ₂₆ N ₂ O
324699	H	N(Me) ₂	H	CO ₂ H	H	H	H	N(Me) ₂	C ₂₄ H ₂₆ N ₂ O ₂
324700	H	H	H	OH	H	H	H	OH	C ₁₉ H ₁₆ O ₂
324701	H	H	H	OH	H	Me	H	OH	C ₂₀ H ₁₈ O ₂
324702	H	H	N(Me) ₂	H	H	H	N(Me) ₂	H	C ₂₃ H ₂₆ N ₂

SOURCE – Cytokinetics.

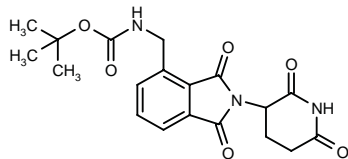
REFERENCES

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CANCER IMMUNOTHERAPY

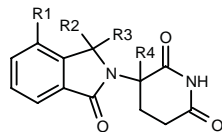
325160

N-[2-(2,6-Dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1 *H*-isoindol-4-ylmethyl]carbamic acid *tert*-butyl ester



C19 H21 N3 O6; Mol wt: 387.3899

ACTION – Agent able to inhibit the production of TNF- α , IL-1 β , IL-10 and/or T-cells, claimed for use in the treatment of cancer, inflammatory disorders such as rheumatoid arthritis, osteoarthritis and heart diseases. Other exemplified isoindole-imide compounds include the following:



Compound	R1	R2	R3	R4	Formula
325161	t-BuCH ₂ CONHCH ₂	-O-		H	C ₂₀ H ₂₃ N ₃ O ₅
325162	CH ₂ NHCO(CH ₂) ₅ CO ₂ Et	-O-		H	C ₂₃ H ₂₇ N ₃ O ₇
325163	2-Pyr-CONH	-O-		H	C ₁₉ H ₁₄ N ₄ O ₅
325164	NHCOPr	-O-		H	C ₁₇ H ₁₇ N ₃ O ₅
325165	cyclopentyl-CONH	-O-		H	C ₁₉ H ₁₉ N ₃ O ₅
325166	NHCOC ₆ H ₁₃	H	H	H	C ₂₀ H ₂₅ N ₃ O ₄
325167	NHCOC ₆ H ₁₃	-O-		Me	C ₂₁ H ₂₅ N ₃ O ₅
325168	CH ₂ NHCONHEt	H	H	H	C ₁₇ H ₂₀ N ₄ O ₄

SOURCE – Celgene.

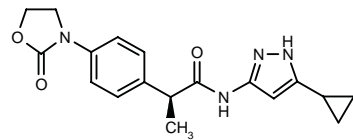
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1. Robarge, M.J. et al. (Celgene Corp.) *Isoindole-imide cpds., compsns., and uses thereof*. WO 0259106.

INHIBITORS OF SIGNAL TRANSDUCTION PATHWAYS

323085

N-(5-Cyclopropyl-1 *H*-pyrazol-3-yl)-2(*S*)-[4-(2-oxo-oxazolidin-3-yl)phenyl]propionamide



C18 H20 N4 O3; Mol wt: 340.3810

ACTION – Cyclin-dependent kinase (CDK) inhibitor that displayed an IC₅₀ of 8 nM against CDK2/cyclin A. Potentially useful for the treatment of cancer and other proliferative disorders such as benign prostatic hyperplasia, familial adenomatosis polyposis, neurofibromatosis, psoriasis, vascular smooth muscle cell proliferation associated with atherosclerosis, pulmonary fibrosis, arthritis, glomerulonephritis and restenosis, and also for the prevention and treatment of radiotherapy- or chemotherapy-induced alopecia.

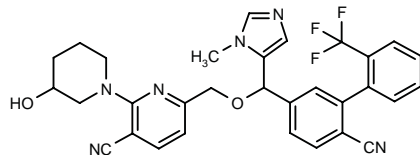
SOURCE – Pharmacia.

REFERENCES

1. Pevarello, P. et al. (Pharmacia & Upjohn SpA) *Phenylacetamido-pyrazole derivs. and their use as antitumor agents*. US 6455559, WO 0248114.

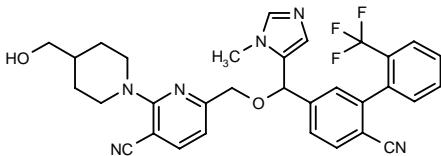
324065

6-[1-[6-Cyano-2'-(trifluoromethyl)biphenyl-3-yl]-1-(1-methyl-1 *H*-imidazol-5-yl)methoxymethyl]-2-(3-hydroxypiperidin-1-yl)pyridine-3-carbonitrile



C31 H27 F3 N6 O2; Mol wt: 572.5883

ACTION – Antineoplastic agent, a potent protein farnesyl-transferase inhibitor (IC₅₀ = 1.3 nM) with high selectivity over protein geranylgeranyltransferase (IC₅₀ = 1400 nM) and activity in a ras processing assay (IC₅₀ = 13 nM). Another related compound is:



324066: C32 H29 F3 N6 O2

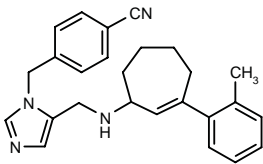
SOURCE – Abbott.

REFERENCES

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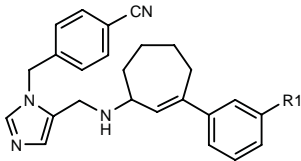
324520

4-[5-[3-(2-Methylphenyl)-2-cyclohepten-1-ylaminomethyl]-1H-imidazol-1-ylmethyl]benzonitrile



C26 H28 N4; Mol wt: 396.5352

ACTION – Selective inhibitor of protein farnesyltransferase with potential in the treatment of cancer, post-angioplasty restenosis and type 1 neurofibromatosis. Other specifically claimed cycloheptene derivatives are:



Compound	R1	Formula
324521	Me	C ₂₆ H ₂₈ N ₄
324522	Cl	C ₂₅ H ₂₅ ClN ₄

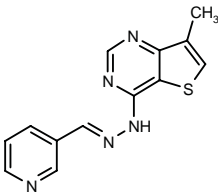
SOURCE – Servier.

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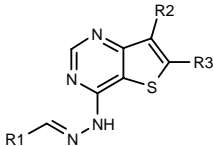
324605

Pyridine-3-carbaldehyde (7-methylthieno[3,2-d]pyrimidin-4-yl)hydrazone



C13 H11 N5 S; Mol wt: 269.3309

ACTION – Src kinase inhibitor giving IC₅₀ values of 0.37, 0.59 and 0.28 μM, respectively, against the N6, N12 and N23 neuronal variants of Src kinases. It also inhibited the proliferation of human colon adenocarcinoma HT-29 cells with an IC₅₀ of 13 μM. Potentially useful for the treatment of cancer, bacterial and viral infections, hematological diseases, osteoporosis, Alzheimer's disease, epilepsy, lupus erythematosus and anaphylaxis. Other exemplified thienopyrimidine derivatives are:



Compound	R1	R2	R3	Formula
324606	2-thienyl	Me	H	C ₁₂ H ₁₀ N ₄ S ₂
324607	3-OH-4-MeO-Ph	Me	H	C ₁₈ H ₁₄ N ₄ O ₂ S
324608	3-Pyr	H	Ph	C ₁₈ H ₁₃ N ₅ S

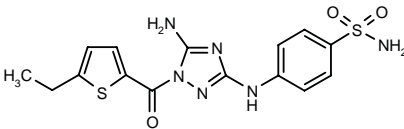
SOURCE – University of Texas System, Austin, TX (US).

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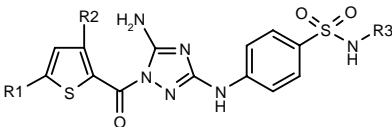
324620

4-[5-Amino-1-(5-ethylthien-2-ylcarbonyl)-1H-1,2,4-triazol-3-ylamino]benzenesulfonamide



C15 H16 N6 O3 S2; Mol wt: 392.4624

ACTION – Inhibitor of cyclin-dependent kinases (CDK) and tyrosine kinases with *in vitro* activity against CDK1, casein kinases, ERK2, VEGF (vascular endothelial growth factor), GSK-3, PDGF (platelet-derived growth factor) and HER2. Compound also exhibited antiproliferative activity against HeLa (IC₅₀ = 71 nM), HCT 116 (IC₅₀ = 26 nM), MDA-MB-231 (IC₅₀ = 131 nM) and PC-3 cells (IC₅₀ = 30 nM). Potentially useful for the treatment of cancer, angiopathy, angiogenesis, chemotherapy-induced alopecia and restenosis. Other exemplified substituted triazole diamine derivatives are:



Compound	R1	R2	R3	Formula
324621	Me	Me	H	C ₁₅ H ₁₆ N ₆ O ₃ S ₂
324622	H	Me	H	C ₁₄ H ₁₄ N ₆ O ₃ S ₂
324624	Et	H	CH2CH2N(Me)2	C ₁₉ H ₂₅ N ₇ O ₃ S ₂

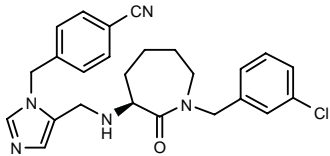
SOURCE – Ortho-McNeil.

REFERENCES

1. Connolly, P.J. et al. (Ortho-McNeil Pharmaceutical, Inc.) *Substd. triazole diamine derivs. as kinase inhibitors*. WO 0257240.

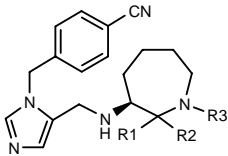
324688

4-[5-[1-(3-Chlorobenzyl)-2-oxoperhydroazepin-3(S)-ylaminomethyl]-1*H*-imidazol-1-ylmethyl]benzonitrile



C25 H26 Cl N5 O; Mol wt: 447.9674

ACTION – Protein farnesyltransferase inhibitor expected to be useful for the treatment of cancer, postangioplasty restenosis and type 1 neurofibromatosis. Other specifically claimed azepane derivatives are:



Compound	R1	R2	R3	Formula
324703		-O-	CH2Ph	C ₂₅ H ₂₇ N ₅ O
324704		-O-	2-Me-PhCH2	C ₂₆ H ₂₉ N ₅ O
324705		-O-	2-Cl-PhCH2	C ₂₅ H ₂₆ ClN ₅ O
324707	H	H	2-Cl-PhCH2	C ₂₅ H ₂₈ ClN ₅
324708	H	H	Ph	C ₂₄ H ₂₇ N ₅

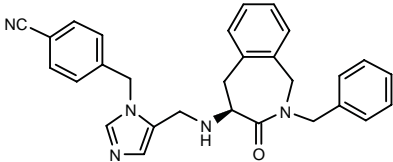
SOURCE – Servier.

REFERENCES

1. Casara, P. et al. (Servier Laboratoires) *Novel azepane cpds., preparation method therefor and pharmaceutical compsns. containing said cpds.* FR 2819511, WO 0257223.

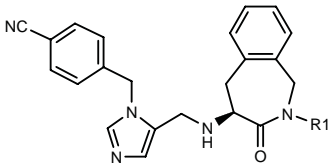
324712

4-[5-[2-Benzyl-3-oxo-2,3,4,5-tetrahydro-1*H*-2-benzazepin-4(S)-ylaminomethyl]-1*H*-imidazol-1-ylmethyl]benzonitrile

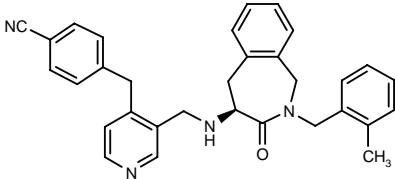


C29 H27 N5 O; Mol wt: 461.5663

ACTION – Protein farnesyltransferase inhibitor expected to be useful for the treatment of cancer, postangioplasty restenosis and type 1 neurofibromatosis. Other specifically claimed cyclo[c]azepane derivatives are:



Compound	R1	Formula
324714	2-Me-PhCH2	C ₃₀ H ₂₉ N ₅ O
324715	Ph	C ₂₈ H ₂₅ N ₅ O



324717: C32 H30 N4 O

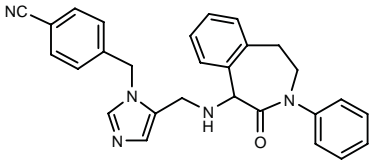
SOURCE – Servier.

REFERENCES

1. Casara, P. et al. (Servier Laboratoires) *Cyclo[c]azepane derivs. which are used as farnesyltransferase inhibitors and method for the preparation therefor.* FR 2819510, WO 0257257.

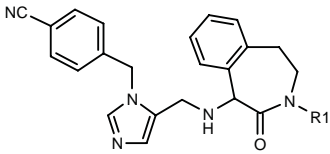
324728

4-[5-(2-Oxo-3-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-1-ylaminomethyl)-1*H*-imidazol-1-ylmethyl]benzonitrile



C28 H25 N5 O; Mol wt: 447.5395

ACTION – Protein farnesyltransferase inhibitor expected to be useful for the treatment of cancer, postangioplasty restenosis and type 1 neurofibromatosis. Other specifically claimed cyclo[d]azepane derivatives are:



Compound	R1	Formula
324729	2-Me-PhCH2	C ₃₀ H ₂₉ N ₅ O
324730	2-Me-Ph	C ₂₉ H ₂₇ N ₅ O

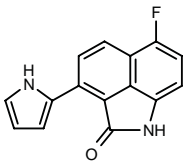
SOURCE – Servier.

REFERENCES

1. Casara, P. et al. (Servier Laboratoires) *Cyclo[d]azepane derivs. which are used as farnesyltransferase inhibitors and method for the separation thereof.* FR 2819512, WO 0257258.

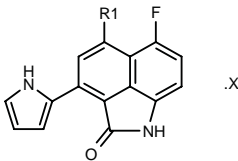
324994

6-Fluoro-3-(1*H*-pyrrol-2-yl)benzo[*cd*]indol-2(1*H*)-one

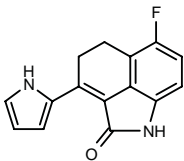


C15 H9 F N2 O; Mol wt: 252.2471

ACTION – Cyclin-dependent kinase CDK2 inhibitor (IC₅₀ < 10 μM), found to inhibit the proliferation of breast carcinoma MDA-MB-435 and colon carcinoma RKO cells (IC₅₀ < 10 μM). Potentially useful as an antitumor agent, particularly in the treatment of breast, colon, lung and prostate cancer. Other exemplified compounds are:



Compound	R1	X	Formula
324995	OMe		C ₁₆ H ₁₁ FN ₂ O ₂
324997	4-morpholinyl		C ₁₉ H ₁₆ FN ₃ O ₂
324998	OCH2CH2OH		C ₁₇ H ₁₃ FN ₂ O ₃
324999	NHCH2CH2NH2		C ₁₇ H ₁₅ FN ₄ O
325000	NHCH2CH2NH2	CF3CO2H	C ₁₇ H ₁₅ FN ₄ O.C ₂ HF ₃ O ₂
325001	NHCH2CH2NH2	MeSO3H	C ₁₇ H ₁₅ FN ₄ O.CH ₄ O ₃ S
325002	NHCH2CH2OH		C ₁₇ H ₁₄ FN ₃ O ₂



324996: C15 H11 F N2 O

SOURCE – Roche.

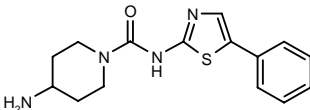
REFERENCES

1. Chen, Y. et al. (F. Hoffmann-La Roche AG) *Naphthostyrils*. WO 0259109.

ANGIOGENESIS INHIBITORS

323757

4-Amino-*N*-(5-phenylthiazol-2-yl)piperidine-1-carbox-amide



C15 H18 N4 O S; Mol wt: 302.4002

ACTION – Potential antiangiogenic agent, a potent inhibitor of protein tyrosine kinase KDR (IC₅₀ = 35 nM) with a good pharmacokinetic profile after oral administration to rats (F = 61%, t_{1/2} = 5 h at 10 mg/kg) and dogs (F = 25%, t_{1/2} = 5.4 h at 1 mg/kg).

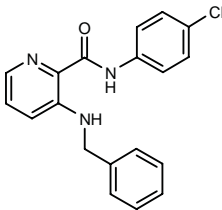
SOURCE – Merck & Co.

REFERENCES

1. Tucker, T.J. et al. *Synthesis and biological evaluation of a series of novel and potent inhibitors of KDR kinase*. 224th ACS Natl Meet (Aug 18-22, Boston) 2002, Abst MEDI 220.

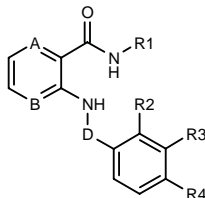
324293

3-(Benzylamino)-*N*-(4-chlorophenyl)pyridine-2-carbox-amide



C19 H16 Cl N3 O; Mol wt: 337.8084

ACTION – An inhibitor of kinases such as vascular endothelial growth factor receptor 2 (VEGFR-2 or EGF/KDR), potentially useful for the treatment of angiogenesis-related disorders, particularly cancer. Other exemplified substituted arylamine derivatives include the following:



Compound	R1	R2	R3	R4	A	B	D	Formula
324294	3-CF3-Ph	F	F	H	CH	N	CH2	C ₂₀ H ₁₄ F ₅ N ₃ O
324295	4-[1-Me-4-Pip-C(Me)2]-Ph	H	H	F	CH	N	CH2	C ₂₈ H ₃₃ FN ₄ O
324296	6-isoquinolinyl	H	H	OMe	CH	N	CH2	C ₂₃ H ₂₀ N ₄ O ₂
324298	5-benzofuryl	H	CH2OH	H	CH	N	CH2	C ₂₂ H ₁₉ N ₃ O ₃
324300	5-benzimidazolyl	H	H	NH2	N	CH	CH2	C ₂₀ H ₁₈ N ₆ O
324303	6-quinazolinyl	H	NH2	H	N	CH	CH2	C ₂₁ H ₁₈ N ₆ O
324304	3-Cl-Ph	H	H	F	CH	N	SO2	C ₁₈ H ₁₃ ClFN ₃ O ₃ S
324305	4-Cl-3-(3-azetidiny-CH2O)-Ph	H	H	F	CH	N	CH2	C ₂₃ H ₂₂ ClFN ₄ O ₂

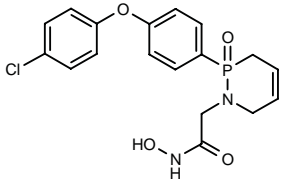
SOURCE – Amgen.

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1. Chen, G. et al. (Amgen Inc.) *Substd. arylamine derivs. and methods of use*. WO 0255501.

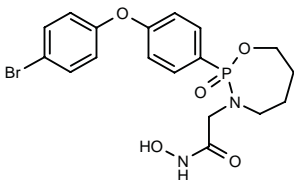
324443

(±)-2-[2-[4-(4-Chlorophenoxy)phenyl]-2-oxido-3,6-dihydro-1,2-azaphosphinin-1(2*H*)-yl]acetohydroxamic acid



C18 H18 Cl N2 O4 P; Mol wt: 392.7772

ACTION – Antineoplastic agent, a potent inhibitor of the matrix metalloproteinases MMP-2 (gelatinase A; IC₅₀ = 4.0 nM) and MMP-9 (gelatinase B; IC₅₀ = 1.4 nM), with high selectivity over MMP-1 (interstitial collagenase; IC₅₀ = 2.9 μM). *In vivo*, compound was at least as effective as prinomastat in suppressing HT-1080 tumor growth in mice and exhibited a favorable pharmacokinetic profile. Another related compound is:



324442: C18 H20 Br N2 O5 P

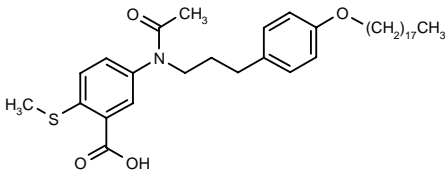
SOURCE – Leo.

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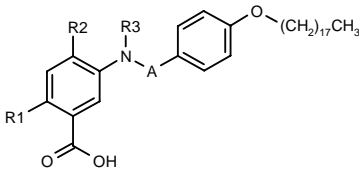
324817

5-[*N*-Acetyl-*N*-[3-[4-(octadecyloxy)phenyl]propyl]amino]-2-(methylsulfonyl)benzoic acid



C37 H57 N O4 S; Mol wt: 611.9263

ACTION – Vascular endothelial growth factor receptor (VEGFR) antagonist (IC₅₀ = 0.18 μM), potentially useful for the treatment of angiogenesis-related disorders including diabetic retinopathy, rheumatoid arthritis, cancer and arteriosclerosis. Other exemplified substituted benzoic acid derivatives are:



Compound	R1	R2	R3	A	Formula
324818	SMe	H	Ac	-CH2-	C ₃₅ H ₅₃ NO ₄ S
324819	SMe	H	SO2Me	-CH2-	C ₃₄ H ₅₃ NO ₅ S ₂
324820	SMe	H	COCH2OMe	-CH2-	C ₃₆ H ₅₅ NO ₅ S
324821	SMe	H	Ac	-(CH2)2-	C ₃₆ H ₅₅ NO ₄ S
324822	H	SMe	Ac	-(CH2)3-	C ₃₇ H ₅₇ NO ₄ S
324823	SMe	H	H	-(CH2)3-	C ₃₅ H ₅₅ NO ₃ S
324824	SMe	H	Me	-(CH2)3-	C ₃₆ H ₅₇ NO ₃ S
324826	SMe	H	COCH2OMe	-(CH2)3-	C ₃₈ H ₅₉ NO ₅ S
324827	SMe	H	2-furyl-CO	-(CH2)3-	C ₄₀ H ₅₇ NO ₅ S
324828	SMe	H	SO2Me	-(CH2)3-	C ₃₆ H ₅₇ NO ₅ S ₂
324829	SMe	H	CHO	-(CH2)3-	C ₃₆ H ₅₅ NO ₄ S
324830	SMe	H	COCH2Ac	-(CH2)3-	C ₃₉ H ₅₉ NO ₅ S

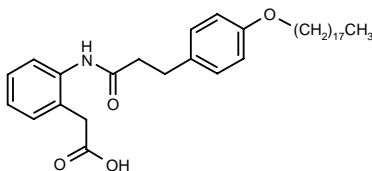
SOURCE – Taisho.

REFERENCES

1. Wada, H. et al. (Taisho Pharmaceutical Co., Ltd.) *Substd. benzoic acid derivs*. JP 2002193922.

324831

2-[2-[3-[4-(Octadecyloxy)phenyl]propionamido]phenyl]-acetic acid



C35 H53 N O4; Mol wt: 551.8067

ACTION – Vascular endothelial growth factor receptor (VEGFR) antagonist (IC₅₀ = 0.31 μM), potentially useful for the treatment of angiogenesis-related disorders including diabetic retinopathy, rheumatoid arthritis, cancer and arteriosclerosis.

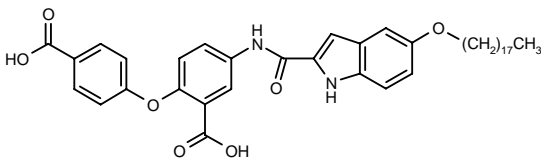
SOURCE – Taisho.

REFERENCES

1. Wada, H. et al. (Taisho Pharmaceutical Co., Ltd.) *Aminophenyl acetic acid derivs*. JP 2002193801.

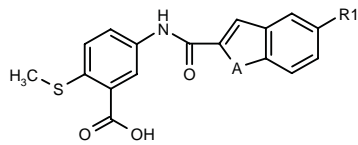
324832

2-(4-Carboxyphenoxy)-5-[5-(octadecyloxy)-1*H*-indol-2-yl]carboxamido]benzoic acid

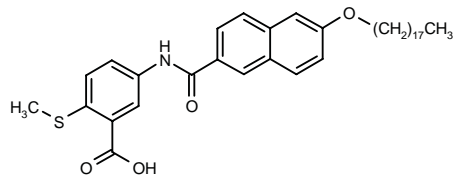


C41 H52 N2 O7; Mol wt: 684.8688

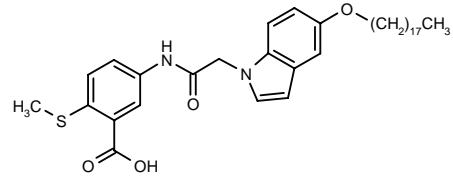
ACTION – Vascular endothelial growth factor receptor (VEGFR) antagonist (IC_{50} = 0.23 μ M), potentially useful for the treatment of angiogenesis-related disorders including diabetic retinopathy, rheumatoid arthritis, cancer and arteriosclerosis. Other exemplified benzoic acid derivatives are:



Compound	R1	A	Formula
324834	OC18H37	NH	C ₃₅ H ₅₀ N ₂ O ₄ S
324837	NHCOC17H35	O	C ₃₅ H ₄₈ N ₂ O ₅ S



324833: C37 H51 N O4 S



324835: C36 H52 N2 O4 S

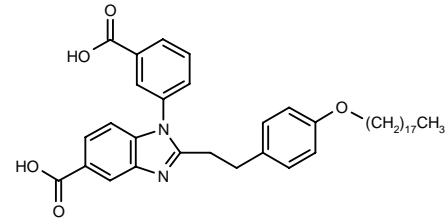
SOURCE – Taisho.

REFERENCES

1. Wada, H. et al. (Taisho Pharmaceutical Co., Ltd.) *Amino benzoic acid derivs.* JP 2002193923.

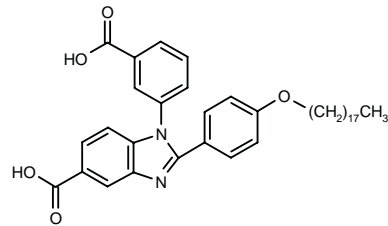
324840

1-(3-Carboxyphenyl)-2-[2-[4-(octadecyloxy)phenyl]ethyl]-1*H*-benzimidazole-5-carboxylic acid



C41 H54 N2 O5; Mol wt: 654.8866

ACTION – Vascular endothelial growth factor receptor (VEGFR) antagonist (IC_{50} = 0.53 μ M), potentially useful for the treatment of angiogenesis-related disorders including diabetic retinopathy, rheumatoid arthritis, cancer and arteriosclerosis. Another exemplified benzimidazole derivative is:



324841: C39 H50 N2 O5

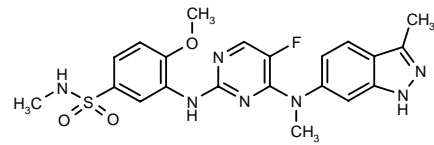
SOURCE – Taisho.

REFERENCES

1. Wada, H. et al. (Taisho Pharmaceutical Co., Ltd.) *Benzimidazole derivs.* JP 2002193947.

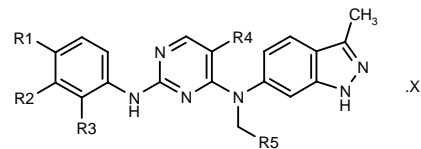
324881

3-[5-Fluoro-4-[*N*-methyl-*N*-(3-methyl-1*H*-indazol-6-yl)-amino]pyrimidin-2-ylamino]-4-methoxy-*N*-methylbenzenesulfonamide

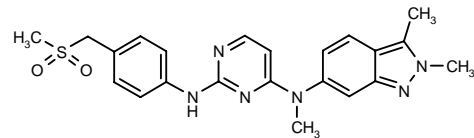


C21 H22 F N7 O3 S; Mol wt: 471.5148

ACTION – Vascular endothelial growth factor receptor-2 (VEGFR-2) kinase inhibitor shown to inhibit the proliferation of human umbilical vein endothelial cells (HUVEC) with an IC_{50} < 200 nM. Potentially useful as an antiangiogenic agent for the treatment of cancer. Other exemplified pyrimidine-2,4-diamine derivatives are:



Compound	R1	R2	R3	R4	R5	X	Formula
324882	H	SO2Me	H	F	H		C ₂₀ H ₁₉ FN ₆ O ₂ S
324883	H	i-PrSO2CH2	H	F	H		C ₂₃ H ₂₅ FN ₆ O ₂ S
324884	SO2NH2	H	OMe	F	H		C ₂₀ H ₂₀ FN ₇ O ₃ S
324885	H	SO2NH2	H	H	H	HCl	C ₁₉ H ₁₉ N ₇ O ₂ S.HCl
324886	H	NHSO2Me	H	H	H		C ₂₀ H ₂₁ N ₇ O ₂ S
324887	H	NHAc	H	H	H		C ₂₁ H ₂₁ N ₇ O
324888	H	CH2SO2Me	H	H	CN		C ₂₂ H ₂₁ N ₇ O ₂ S
324889	SO2NH2	H	OMe	H	H		C ₂₀ H ₂₁ N ₇ O ₃ S
324890	Cl	SO2NH2	H	H	H		C ₁₉ H ₁₈ ClN ₇ O ₂ S



324891: C22 H24 N6 O2 S

SOURCE – GlaxoSmithKline.

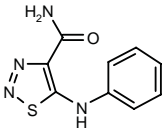
REFERENCES

1. Bloor, A. et al. (GlaxoSmithKline plc) *Pyrimidineamines as angiogenesis modulators*. WO 0259110.

KP-15807

324767

5-(Phenylamino)-1,2,3-thiadiazole-4-carboxamide



C9 H8 N4 O S; Mol wt: 220.2552

ACTION – A representative compound within a series of 1,2,3-thiadiazole-4-carboxamide derivatives that act as protein kinase inhibitors. KP-15807 inhibited integrin-linked kinase (ILK) *in vitro* with an IC₅₀ of 1 μM. It was also found to be active in cell-based angiogenesis and invasion assays, as well as in a murine tumor allograft model following i.p. administration. Potentially useful for the treatment of cancer and other angiogenesis-related disorders.

SOURCE – Kinetek.

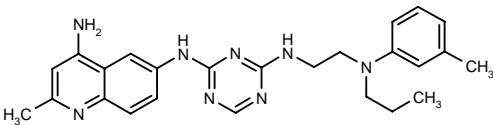
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OTHER ONCOLYTIC DRUGS

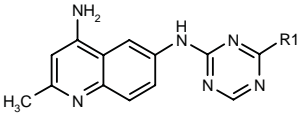
324297

2-Methyl-*N*⁶-[4-[2-[*N*-(3-methylphenyl)-*N*-propyl-amino]ethylamino]-1,3,5-triazin-2-yl]quinoline-4,6-diamine



C25 H30 N8; Mol wt: 442.5680

ACTION – Antitumor agent with telomerase-inhibitory activity. Compound displayed an IC₅₀ of 0.86 μM against telomerase and inhibited the growth of lung cancer A549 cells with an IC₅₀ < 0.3 μM. Other exemplified compounds are:



Compound	R1	Formula
324299	1-Me-4-Pip-NH	C ₁₉ H ₂₄ N ₈
324301	1-[NH2C(=NH)]-4-Pip-CH2NH	C ₂₀ H ₂₆ N ₁₀
324302	4-Me-perhydro-1,4-diazepin-1-yl	C ₁₉ H ₂₄ N ₈

SOURCE – Aventis Pharma.

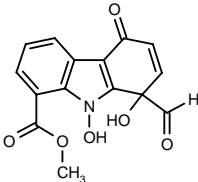
REFERENCES

1. Mailliet, P. et al. (Aventis Pharma SA) *Chemical derivs. and their use as anti-telomerase agent*. FR 2819255, WO 0255515.

COPROVERDINE

323088

1-Formyl-1,9-dihydroxy-4-oxo-4,9-dihydro-1*H*-carbazole-8-carboxylic acid methyl ester



C15 H11 N O6; Mol wt: 301.2529

ACTION – Antitumor agent isolated from an ascidian that displayed antiproliferative activity against murine leukemia P388 cells (IC₅₀ = 1.6 μM), human lung cancer A549 cells (IC₅₀ = 0.3 μM), colon cancer HT-29 cells (IC₅₀ = 0.3 μM), melanoma MEL-28 cells (IC₅₀ = 0.3 μM) and prostate cancer DU 145 cells (IC₅₀ = 0.3 μM). Particularly useful for the treatment of lung cancer, prostate cancer, colon cancer and melanoma.

SOURCE – PharmaMar.

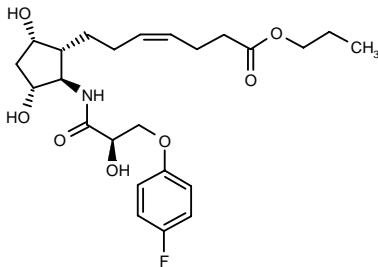
REFERENCES

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OCULAR MEDICATIONS

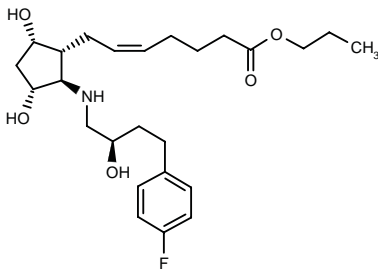
324263

7-[(1*R*,2*R*,3*R*,5*S*)-2-[3-(4-Fluorophenoxy)-2(*R*)-hydroxypropionamido]-3,5-dihydroxycyclopentyl]-4(*Z*)-heptenoic acid propyl ester



C24 H34 F N O7; Mol wt: 467.5306

ACTION – Prostaglandin analogue for the treatment of glaucoma and ocular hypertension, reported to exhibit an improved profile when compared to natural prostaglandins and many of their known analogues. Another specifically claimed 13-aza-prostaglandin is:



324264: C25 H38 F N O5

SOURCE – Alcon.

REFERENCES

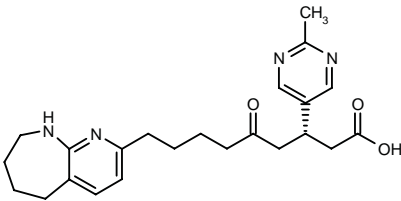
1. Klimko, P.G. (Alcon Laboratories, Inc.) *13-Aza prostaglandins for the treatment of glaucoma and ocular hypertension*. US 6417228.

METABOLIC DRUGS

TREATMENT OF BONE DISEASES

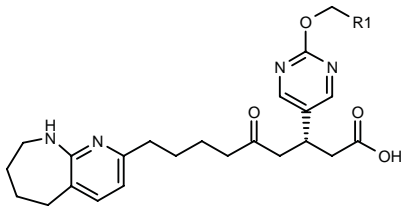
323131

3(*S*)-(2-Methylpyrimidin-5-yl)-5-oxo-9-(6,7,8,9-tetrahydro-5*H*-pyrido[2,3-*b*]azepin-2-yl)nonanoic acid



C23 H30 N4 O3; Mol wt: 410.5150

ACTION – Antagonist at $\alpha_v\beta_3$ and/or $\alpha_v\beta_5$ integrin receptors, potentially useful for the treatment of osteoporosis, as well as restenosis, angiogenesis, diabetic retinopathy, macular degeneration and arthritis. Other specifically claimed compounds are:



Compound	R1	Formula
323132	H	C ₂₃ H ₃₀ N ₄ O ₄
323133	Me	C ₂₄ H ₃₂ N ₄ O ₄

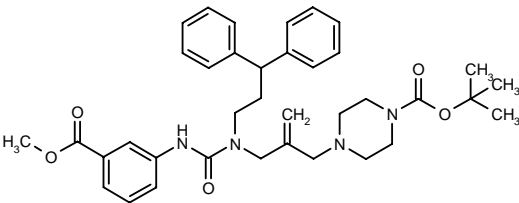
SOURCE – Merck & Co.

REFERENCES

1. Duggan, M.E. et al. (Merck & Co., Inc.) *α_v Integrin receptor antagonists*. US 6410526.

325173

4-[2-[1-(3,3-Diphenylpropyl)-3-[3-(methoxycarbonyl)-phenyl]ureidomethyl]-2-propenyl]piperazine-1-carboxylic acid *tert*-butyl ester

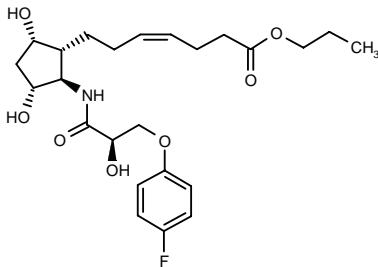


C37 H46 N4 O5; Mol wt: 626.7934

OCULAR MEDICATIONS

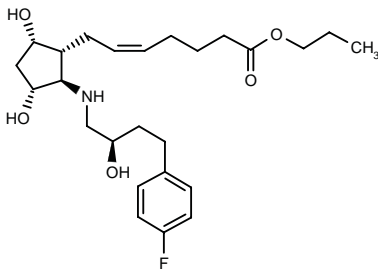
324263

7-[(1*R*,2*R*,3*R*,5*S*)-2-[3-(4-Fluorophenoxy)-2(*R*)-hydroxypropionamido]-3,5-dihydroxycyclopentyl]-4(*Z*)-heptenoic acid propyl ester



C24 H34 F N O7; Mol wt: 467.5306

ACTION – Prostaglandin analogue for the treatment of glaucoma and ocular hypertension, reported to exhibit an improved profile when compared to natural prostaglandins and many of their known analogues. Another specifically claimed 13-aza-prostaglandin is:



324264: C25 H38 F N O5

SOURCE – Alcon.

REFERENCES

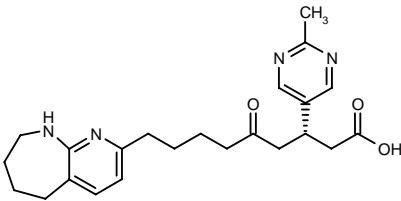
1. Klimko, P.G. (Alcon Laboratories, Inc.) *13-Aza prostaglandins for the treatment of glaucoma and ocular hypertension*. US 6417228.

METABOLIC DRUGS

TREATMENT OF BONE DISEASES

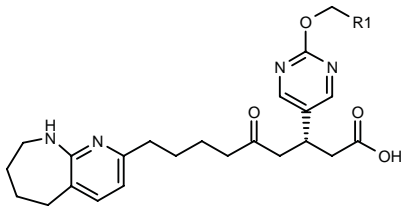
323131

3(*S*)-(2-Methylpyrimidin-5-yl)-5-oxo-9-(6,7,8,9-tetrahydro-5*H*-pyrido[2,3-*b*]azepin-2-yl)nonanoic acid



C23 H30 N4 O3; Mol wt: 410.5150

ACTION – Antagonist at $\alpha_v\beta_3$ and/or $\alpha_v\beta_5$ integrin receptors, potentially useful for the treatment of osteoporosis, as well as restenosis, angiogenesis, diabetic retinopathy, macular degeneration and arthritis. Other specifically claimed compounds are:



Compound	R1	Formula
323132	H	C ₂₃ H ₃₀ N ₄ O ₄
323133	Me	C ₂₄ H ₃₂ N ₄ O ₄

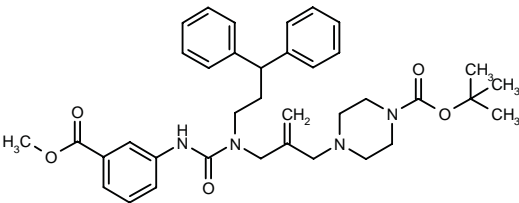
SOURCE – Merck & Co.

REFERENCES

1. Duggan, M.E. et al. (Merck & Co., Inc.) *α_v Integrin receptor antagonists*. US 6410526.

325173

4-[2-[1-(3,3-Diphenylpropyl)-3-[3-(methoxycarbonyl)-phenyl]ureidomethyl]-2-propenyl]piperazine-1-carboxylic acid *tert*-butyl ester



C37 H46 N4 O5; Mol wt: 626.7934

ACTION – Calcium receptor modulator, a representative compound from a series of urea derivatives, potentially useful for the treatment of hypercalcemia, hyperparathyroidism and osteoporosis, among other disorders associated with calcium metabolism.

SOURCE – Aventis Pharma.

REFERENCES

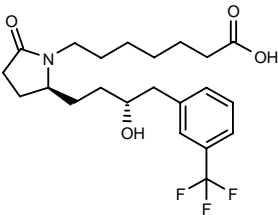
1. Deprez, P. and Patek, M. (Aventis Pharma SA) *Novel urea derivs., method for preparing same, use thereof as medicines, pharmaceutical compsns. and novel use.* FR 2820136, WO 0259102.

CMP-3¹⁻³

324006

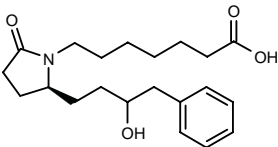
7-[2(*S*)-[3(*R*)-Hydroxy-4-[3-(trifluoromethyl)phenyl]butyl]-5-oxopyrrolidin-1-yl]heptanoic acid

CP-B



C22 H30 F3 N O4; Mol wt: 429.4760

ACTION – Potent and selective prostanoid EP₄ receptor agonist with nanomolar affinity for EP₄ receptors (IC₅₀ = 21 nM), high selectivity over EP₂ receptors (IC₅₀ > 2700 nM) and potent agonist activity in functional experiments (EC₅₀ = 13 nM). In an osteopenic rat model using ovariectomized rats, doses of 3-30 mg/kg/day s.c. for 4 weeks produced increases in total bone content, total density, cortical content and cortical area. Potentially useful for the treatment of osteoporosis. Another related compound is:



CMP-2 [324005]¹⁻⁴: C21 H31 N O4
CP-A

SOURCE – Pfizer.

REFERENCES

1. Cameron, K.O. et al. (Pfizer Products Inc.) *EP4 receptor selective agonists in the treatment of osteoporosis.* EP 1110949, JP 2001181210, WO 0146140.

2. Cameron, K.O. et al. *Discovery and bone anabolic activity of highly selective EP4 receptor prostaglandin E2 (PGE2) agonists.* 224th ACS Natl Meet (Aug 18-22, Boston) 2002, Abst MEDI 307.

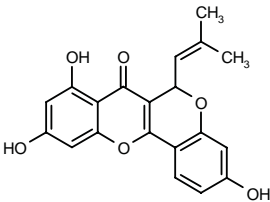
3. Cameron, K.O. et al. *Discovery of highly selective EP4 receptor prostaglandin E2 (PGE2) agonists which stimulate new bone formation and restore bone mass in ovariectomized rats.* J Bone Miner Res 2002, 17(Suppl. 1): Abst M397.

4. Ke, H.Z. et al. *A non-prostanoid EP4 receptor selective prostaglandin E2 (PGE2) agonist stimulates bone formation and restores bone mass and strength in ovariectomized rats.* J Bone Miner Res 2002, 17(Suppl. 1): Abst M392.

CYCLOCOMMUNOL

325145

3,8,10-Trihydroxy-6-(2-methyl-1-propenyl)-6,7-dihydro[1]-benzopyrano[4,3-*b*][1]benzopyran-7-one



C20 H16 O6; Mol wt: 352.3404

ACTION – Estrogen receptor ERβ modulator isolated from the plant *Batocarpus costaricensis*. As an ERβ agonist, compound has potential in the treatment of osteoporosis and hot flushes.

SOURCE – Merck & Co.

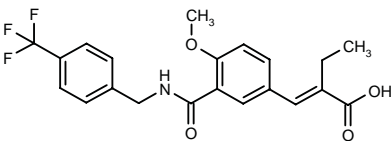
REFERENCES

1. Goetz, M.A. et al. (Merck & Co., Inc.) *Pyranoflavonoid cpds. and their use as estrogen receptor modulators.* WO 0258639.

TREATMENT OF LIPOPROTEIN DISORDERS

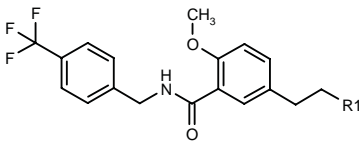
322638

2-Ethyl-3-[4-methoxy-3-[*N*-[4-(trifluoromethyl)benzyl]-carbamoyl]phenyl]-2-propenoic acid



C21 H20 F3 N O4; Mol wt: 407.3860

ACTION – Peroxisome proliferator-activated receptor PPARα agonist with potential in the treatment of metabolic disorders such as hyperlipidemia, arteriosclerosis, diabetes and obesity. Other exemplified substituted carboxylic acid derivatives are:



Compound	R1	Formula
322639	CO2Me	C ₂₀ H ₂₀ F ₃ NO ₄
322640	CO2H	C ₁₉ H ₁₈ F ₃ NO ₄
322641	5-tetrazolyl	C ₁₉ H ₁₈ F ₃ N ₅ O ₂
322642	CH2CO2H	C ₂₀ H ₂₀ F ₃ NO ₄

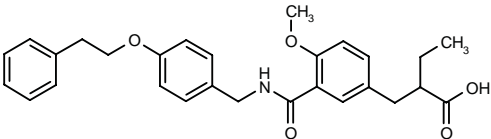
SOURCE – Kyorin.

REFERENCES

1. Miyachi, H. et al. (Kyorin Pharmaceutical Co., Ltd.) *Substd. carboxylic acid derivs.* WO 0244131.

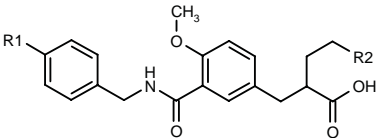
322643

2-[4-Methoxy-3-[N-[4-(2-phenylethoxy)benzyl]carbamoyl]-benzyl]butyric acid



C28 H31 N O5; Mol wt: 461.5549

ACTION – Peroxisome proliferator-activated receptor PPARα agonist with potential in the treatment of metabolic disorders such as hyperlipidemia, arteriosclerosis, diabetes and obesity. Other exemplified substituted carboxylic acid derivatives are:



Compound	R1	R2	Formula
322644	Cl	H	C ₂₀ H ₂₂ ClNO ₄
322645	H	H	C ₂₀ H ₂₃ NO ₄
322646	CH ₂ CH ₂ Ph	H	C ₂₈ H ₃₁ NO ₄
322647	CH ₂ CH ₂ Ph	Me	C ₂₉ H ₃₃ NO ₄

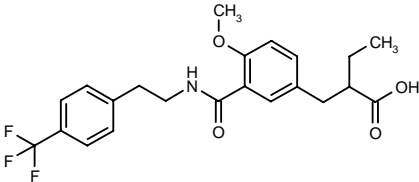
SOURCE – Kyorin.

REFERENCES

1. Miyachi, H. et al. (Kyorin Pharmaceutical Co., Ltd.) *Substd. carboxylic acid derivs.* WO 0244130.

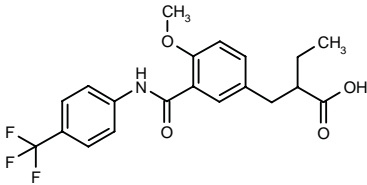
322648

2-[4-Methoxy-3-[N-[2-[4-(trifluoromethyl)phenyl]-ethyl]carbamoyl]benzyl]butyric acid



C22 H24 F3 N O4; Mol wt: 423.4286

ACTION – Peroxisome proliferator-activated receptor PPARα agonist with potential in the treatment of metabolic disorders such as hyperlipidemia, arteriosclerosis, diabetes and obesity. Another exemplified substituted carboxylic acid derivative is:



322649: C20 H20 F3 N O4

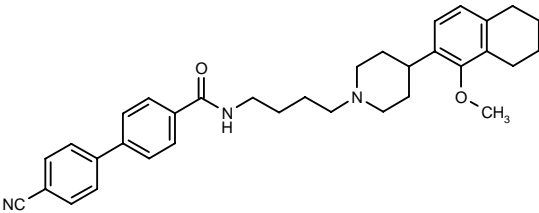
SOURCE – Kyorin.

REFERENCES

1. Miyachi, H. and Murakami, K. (Kyorin Pharmaceutical Co., Ltd.) *Substd. carboxylic acid derivs..* WO 0244129.

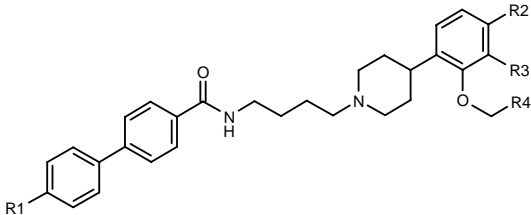
324370

4'-Cyano-N-[4-[4-(1-methoxy-5,6,7,8-tetrahydronaphthalen-2-yl)piperidin-1-yl]butyl]biphenyl-4-carboxamide



C34 H39 N3 O2; Mol wt: 521.7011

ACTION – LDL receptor upregulator proven to induce LDL receptor expression in human hepatocarcinoma cells with an EC₅₀ of 10 nM. In fat-fed hamsters, compound reduced VLDL/LDL cholesterol with an ED₅₀ of 1 mg/kg p.o. Other exemplified compounds are:



Compound	R1	R2	R3	R4	Formula
324371	Cl	-CH=CHCH=CH-	H	H	C ₃₃ H ₃₅ ClN ₂ O ₂
324372	CN	Et	H	Me	C ₃₃ H ₃₉ N ₃ O ₂

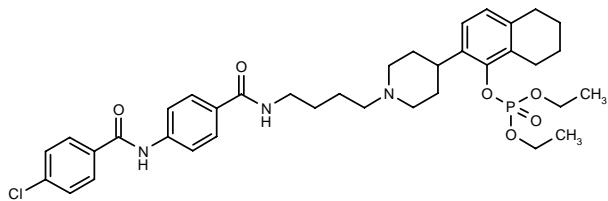
SOURCE – GlaxoSmithKline.

REFERENCES

1. Bouilliot, A.M.J. et al. (GlaxoSmithKline plc) *Aryl piperidine derivs. as inducers of LDL-receptor expression.* WO 0255497.

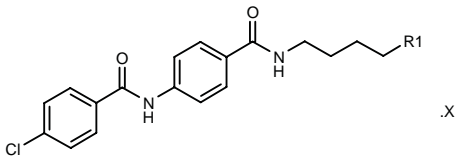
324373

Phosphoric acid 2-[1-[4-[4-(4-chlorobenzamido)benz-amido]butyl]piperidin-4-yl]-5,6,7,8-tetrahydronaphthalen-1-yl diethyl ester



C37 H47 Cl N3 O6 P; Mol wt: 696.2203

ACTION – LDL receptor upregulator proven to induce LDL receptor expression in human hepatocarcinoma cells with an EC₅₀ of 4 nM. In fat-fed hamsters, compound reduced VLDL/LDL cholesterol with an ED₅₀ of 2-5 mg/kg p.o. Other exemplified compounds are:



Compound	R1	X	Formula
324375	5-Me-2-(4-Pip)-PhO	HCl	C ₃₀ H ₃₄ ClN ₃ O ₃ ·HCl
324376	4-(2-AcO-4-Me-Ph)-1-Pip		C ₃₂ H ₃₆ ClN ₃ O ₄
324377	4-[4-Me-2-[PO(OEt)2O]-Ph]-1-Pip		C ₃₄ H ₄₃ ClN ₃ O ₆ P

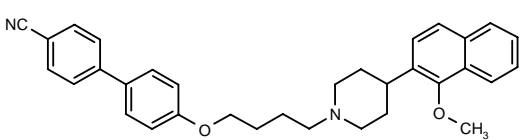
SOURCE – GlaxoSmithKline.

REFERENCES

1. Bouillot, A.M.J. et al. (GlaxoSmithKline plc) *Aryl piperidine derivs. as inducers of LDL-receptor expression*. WO 0255495.

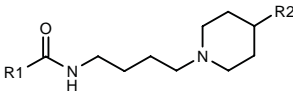
324378

4'-[4-[4-(1-Methoxynaphthalen-2-yl)piperidin-1-yl]butoxy]-biphenyl-4-carbonitrile



C33 H34 N2 O2; Mol wt: 490.6436

ACTION – LDL receptor upregulator proven to induce LDL receptor expression in human hepatocarcinoma cells with an EC₅₀ of 1 nM. Other exemplified compounds are:



Compound	R1	R2	Formula
324379	4-(4-CF3-Ph)-Ph	2,5-(Me)2-4-(2-Pyr-CH2O)-Ph	C ₃₇ H ₄₀ F ₃ N ₃ O ₂
324380	4-(4-CN-Ph)-Ph	1-Me-3-indolyl	C ₃₂ H ₃₄ N ₄ O
324381	4-(4-CF3-Ph)-Ph	2-EtO-4-Me-PhN(SO2Ph)	C ₃₈ H ₄₂ F ₃ N ₃ O ₄ S
324382	4-(4-CF3-PhCH=CH)-Ph	2-EtO-4-Me-Ph	C ₃₄ H ₃₉ F ₃ N ₂ O ₂
324383	2-[3,4-(Cl)2-Ph]-1-benzofuran-5-yl	1-(cyclopropyl-CH2O)-5,6,7,8-tetrahydro-2-Naph	C ₃₈ H ₄₂ Cl ₂ N ₂ O ₃
324384	2-(6-CF3-3-Pyr)-1-benzofuran-5-yl	1-(cyclopropyl-CH2O)-5,6,7,8-tetrahydro-2-Naph	C ₃₈ H ₄₂ F ₃ N ₃ O ₃

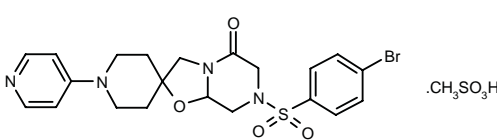
SOURCE – GlaxoSmithKline.

REFERENCES

1. Bouillot, A.M.J. et al. (GlaxoSmithKline plc) *Aryl piperidine and piperazine derivs. as inducers of LDL-receptor expression*. WO 0255496.

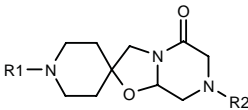
324464

7-(4-Bromophenylsulfonyl)-1'-(4-pyridyl)perhydrospiro-[oxazolo[3,2-a]pyrazin-2,4'-piperidine]-5-one methane-sulfonate



C21 H23 Br N4 O4 S . C H4 O3 S; Mol wt: 603.5123

ACTION – An inhibitor of 2,3-epoxysqualene–lanosterol cyclase (lanosterol synthase) found to inhibit the bio-synthesis of cholesterol in murine L929 fibroblasts by 44% at 0.3 µg/ml. *In vivo*, oral administration of this compound to rats at a dose of 30 mg/kg resulted in a 26% decrease in serum cholesterol levels. Potentially useful for the treatment of hypercholesterolemia, hyperlipidemia, arteriosclerosis, myocardial infarction, mycosis, etc. Other exemplified tricyclic spiro compounds are:



Compound	R1	R2	Formula
324466	4-pyrimidinyl	4-Br-PhSO2	C ₂₀ H ₂₂ BrN ₅ O ₄ S
324467	4-Pyr	2-Naph-SO2	C ₂₅ H ₂₆ N ₄ O ₄ S
324468	4-Pyr	4-Br-PhCH2	C ₂₂ H ₂₆ BrN ₄ O ₂
324469	4-Br-PhSO2	4-Pyr-CH2	C ₂₂ H ₂₅ BrN ₄ O ₄ S

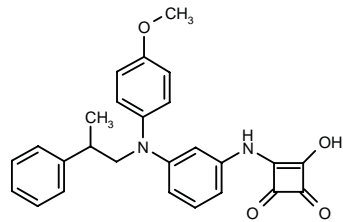
SOURCE – Mochida.

REFERENCES

1. Nishida, H. and Mukaihira, T. (Mochida Pharmaceutical Co., Ltd.) *Cholesterol biosynthesis inhibitors containing as the active ingredient tricyclic spiro cpds*. WO 0253568.

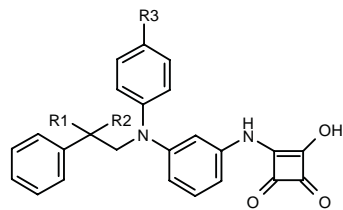
324742

3-Hydroxy-4-[3-[N-(4-methoxyphenyl)-N-(2-phenylpropyl)-amino]phenylamino]-3-cyclobutene-1,2-dione



C26 H24 N2 O4; Mol wt: 428.4856

ACTION – An inhibitor of ileal bile acid transport, as demonstrated in hamster everted ileal rings (57% inhibition at 30 µg/ml). *In vivo*, compound was also found to inhibit bile acid transport by 66% following oral administration to hamsters at a dose of 100 mg/kg. Potentially useful for the treatment of hyperlipidemia and arteriosclerosis. Other exemplified phenylamine derivatives are:



Compound	R1	R2	R3	Formula
324743	H	Me	F	C ₂₆ H ₂₁ FN ₂ O ₃
324744	H	Me	Cl	C ₂₆ H ₂₁ ClN ₂ O ₃
324745	H	OMe	OMe	C ₂₈ H ₂₄ N ₂ O ₅
324746	-CH2-		OMe	C ₂₆ H ₂₂ N ₂ O ₄

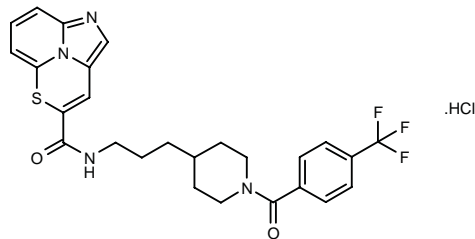
SOURCE – Sankyo.

REFERENCES

1. Kurata, H. et al. (Sankyo Co., Ltd.) *Phenylamine derivs.* JP 2002212152.

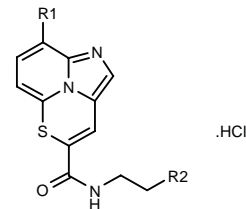
325111

N-[3-[1-[4-(Trifluoromethyl)benzoyl]piperidin-4-yl]propyl]-5-thia-1,8b-diazaacenaphthylene-4-carboxamide hydrochloride



C26 H25 F3 N4 O2 S . HCl; Mol wt: 551.0304

ACTION – Hypolipidemic and hypoglycemic agent with the ability to activate LDL receptors; it was found to promote the expression of the LDL receptor gene in HepG2 cells (384% at 1.1 µM) and it induced an increase (350% at 5 µM) in the binding of [¹²⁵I]-LDL to LDL receptors in these cells. Potentially useful for the treatment of arteriosclerosis, hyperlipidemia, diabetes and complications thereof, arrhythmia, peripheral vascular disease, thrombosis, pancreatic disorders, etc. Other exemplified tricyclic compounds are:



Compound	R1	R2	Formula
325112	H	1-(4-CF3-PhSO2)-4-Pip	C ₂₄ H ₂₃ F ₃ N ₄ O ₃ S ₂ .HCl
325113	H	1-(4-CF3-PhSO2)-4-Pip-CH2	C ₂₅ H ₂₅ F ₃ N ₄ O ₃ S ₂ .HCl
325114	H	1-(4-CF3-PhSO2)-4-Pip-CH2CH2	C ₂₆ H ₂₇ F ₃ N ₄ O ₃ S ₂ .HCl
325115	Me	1-(4-CF3-PhSO2)-4-Pip-CH2	C ₂₆ H ₂₇ F ₃ N ₄ O ₃ S ₂ .HCl
325116	H	1-(4-Br-PhSO2)-4-Pip-CH2	C ₂₄ H ₂₅ BrN ₄ O ₃ S ₂ .HCl
325117	H	1-[2-(4-Cl-PhCH2S)PhCO]-4-Pip-CH2	C ₃₂ H ₃₁ ClN ₄ O ₂ S ₂ .HCl
325118	H	(E)-1-(4-CF3-PhCH=CHCO)-4-Pip-CH2	C ₂₈ H ₂₇ F ₃ N ₄ O ₂ S.HCl

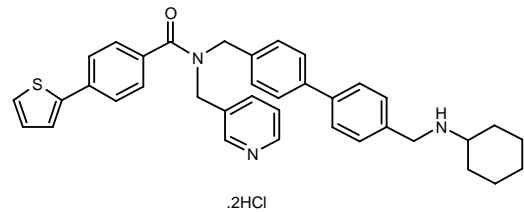
SOURCE – Takeda.

REFERENCES

1. Koori, M. et al. (Takeda Chemical Industries, Ltd.) *Tricyclic cpds., their preparation method and agents.* JP 2002201193.

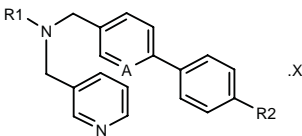
325134

N-[4'-(Cyclohexylaminomethyl)biphenyl-4-ylmethyl]-N-(pyridin-3-ylmethyl)-4-(2-thienyl)benzamide dihydrochloride



C37 H37 N3 O S . 2HCl; Mol wt: 644.7071

ACTION – Hypolipidemic agent, an upregulator of LDL receptors found to promote the expression of the LDL receptor gene in HepG2 cells (320% at 0.37 µM). It also induced an increase in the binding of [¹²⁵I]-LDL to LDL receptors in HepG2 cells (342% at 0.10 µM). Potentially useful for the treatment of arteriosclerosis and hyperlipidemia. Other exemplified biaryl compounds are:



Compound	R1	R2	A	X	Formula
325136	4-CF3-PhNHCO	cyclohexyl-NHCH2	CH	2HCl	C ₃₄ H ₃₅ F ₃ N ₄ O .2HCl
325137	4-Ph-PhSO2	cyclohexyl-NHCH2	CH	2HCl	C ₃₈ H ₃₉ N ₃ O ₂ S .2HCl
325138	4-(PhO)-PhSO2	cyclohexyl-NHCH2	CH	2HCl	C ₃₈ H ₃₉ N ₃ O ₃ S .2HCl
325139	4-(PhOCH2)-PhCO	cyclohexyl-NHCH2	CH	2HCl	C ₄₀ H ₄₁ N ₃ O ₂ .2HCl
325140	4-Ph-PhSO2	cyclohexyl-NHCO	CH		C ₃₈ H ₃₇ N ₃ O ₃ S
325141	4-Ph-PhSO2	t-BuOCONH	CH		C ₃₈ H ₃₅ N ₃ O ₄ S
325142	4-Ph-PhSO2	2-CF3-PhCH2CONH	CH		C ₄₀ H ₃₂ F ₃ N ₃ O ₃ S
325143	4-Ph-PhSO2	cyclohexyl-NHCO	N		C ₃₇ H ₃₆ N ₄ O ₃ S

SOURCE – Takeda.

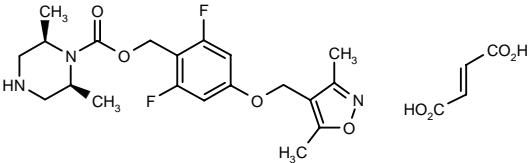
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1. Kori, M. et al. (Takeda Chemical Industries, Ltd.) *Biaryl cpd., process for producing the same, and agent.* WO 0255484.

TREATMENT OF OBESITY AND NUTRITIONAL DISORDERS

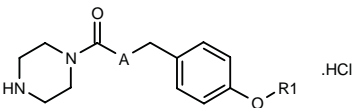
322997

cis-2,6-Dimethylpiperazine-1-carboxylic acid 4-(3,5-dimethylisoxazol-4-ylmethoxy)-2,6-difluorobenzyl ester fumarate



C20 H25 F2 N3 O4 . C4 H4 O4; Mol wt: 525.5021

ACTION – Selective 5-HT_{2C} receptor agonist (EC₅₀ = 22 nM at human 5-HT_{2C} receptors expressed in CHO cells) that exhibits 25-fold selectivity over 5-HT_{2A} receptors. Potentially useful for the treatment of obesity and diabetes. Further applications include CNS disorders such as depression, bipolar disorder, anxiety, sleep disorders, sexual dysfunction, gastrointestinal and cardiovascular disorders, and sleep apnea. Other exemplified piperazine derivatives are:



Compound	R1	A	Formula
322999	CHF2	O	C ₁₃ H ₁₆ F ₂ N ₂ O ₃ .HCl
323000	CH2Ph	S	C ₁₉ H ₂₂ N ₂ O ₂ S.HCl
323001	i-PrNHCO	S	C ₁₆ H ₂₃ N ₃ O ₃ S.HCl

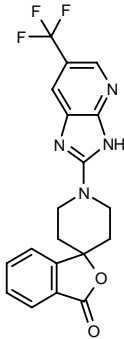
SOURCES – Roche; Vernalis.

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1. Adams, D.R. et al. (F. Hoffmann-La Roche AG;Vernalis Research Ltd.) *Piperazine derivs.* WO 0248124.

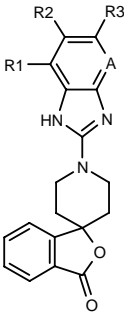
323194

1'-[6-(Trifluoromethyl)-3H-imidazo[4,5-b]pyridin-2-yl]-1,3-dihydrospiro[2-benzofuran-1,4'-piperidin]-3-one



C19 H15 F3 N4 O2; Mol wt: 388.3475

ACTION – Neuropeptide Y (NPY) Y₅ receptor modulator, potentially useful for the treatment of eating disorders, psychiatric disorders, cardiovascular diseases and diabetes. Other specifically claimed spiro[2-benzofuran-1,4'-piperidine] derivatives include the following:



Compound	R1	R2	R3	A	Formula
323195	H	H	SO2Pr	CH	C ₂₂ H ₂₃ N ₃ O ₄ S
323196	H	H	CO2Me	CH	C ₂₁ H ₁₉ N ₃ O ₄
323197	H	H	2-pyrazinyl	CH	C ₂₃ H ₁₉ N ₅ O ₂
323198	H	H	OMe	CH	C ₂₀ H ₁₉ N ₃ O ₃
323199	H	H	SO2Me	CH	C ₂₀ H ₁₉ N ₃ O ₄ S
323200	Cl	H	Cl	CH	C ₁₉ H ₁₅ Cl ₂ N ₃ O ₂
323201	H	OMe	OMe	CH	C ₂₁ H ₂₁ N ₃ O ₄
323202	H	H	Cl	N	C ₁₈ H ₁₅ ClN ₄ O ₂

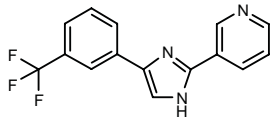
SOURCE – Neurogen.

REFERENCES

1. Bakthavatchalam, R. et al. (Neurogen Corp.) *Spiro[isobenzofuran-1,4'-piperidin]-3-ones and 3H-spiroisobenzofuran-1,4'-piperidines.* WO 0248152.

324068

3-[4-[3-(Trifluoromethyl)phenyl]-1*H*-imidazol-2-yl]pyridine



C15 H10 F3 N3; Mol wt: 289.2590

ACTION – Neuropeptide Y (NPY) Y₅ receptor antagonist (K_i = 3.9 nM against recombinant human receptor) able to inhibit Y₅ agonist-induced feeding in rats (ID₅₀ = 1.6 mg/kg p.o.), as well as to significantly decrease the body weight gain in diet-induced obese rats at a dose of 10 mg/kg p.o. for 28 days. Pharmacokinetic experiments showed that compound was well absorbed after oral administration and provided good brain and cerebrospinal fluid (CSF) levels. Potentially useful for the treatment of obesity.

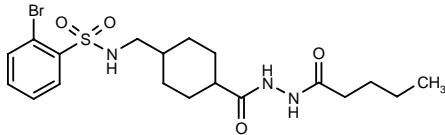
SOURCE – Schering-Plough.

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1. Boyle, C.D. et al. *2,4-Diarylimidazoles as neuropeptide Y Y5 receptor antagonists*. 224th ACS Natl Meet (Aug 18-22, Boston) 2002, Abst MED1 335.

324578

2-Bromo-*N*-[4-(3-pentanoylcarbazoyl)cyclohexylmethyl]-benzenesulfonamide



C19 H28 Br N3 O4 S; Mol wt: 474.4172

ACTION – A representative compound from a series of hydrazide derivatives with affinity for neuropeptide Y (NPY) receptors. Compound was able to induce a 42% reduction in food intake following i.p. administration to rats at a dose of 5 mg/kg. Potentially useful for the treatment of diabetes, obesity, bulimia, anorexia nervosa, arterial hypertension, anxiety, depression, epilepsy, sexual dysfunction and sleep disorders.

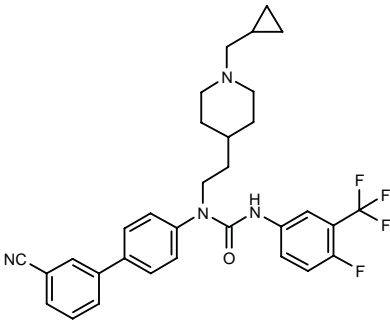
SOURCE – Servier.

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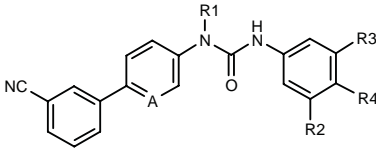
324630

N-(3'-Cyanobiphenyl-4-yl)-*N*-[2-[1-(cyclopropylmethyl)-piperidin-4-yl]ethyl]-*N*'-[4-fluoro-3-(trifluoromethyl)-phenyl]urea



C32 H32 F4 N4 O; Mol wt: 564.6238

ACTION – Melanin-concentrating hormone (MCH) antagonist for the treatment of eating disorders and diabetes, particularly obesity and disorders related therewith. Other specifically claimed compounds include the following:



Compound	R1	R2	R3	R4	A	Formula
324639	(R)-3-MeO-1-pyrrolidinyl-CH2CH2	H	CF3	F	CH	C ₂₈ H ₂₆ F ₄ N ₄ O ₂
324641	(R)-3-(AcNH)-1-pyrrolidinyl-(CH2)4	H	Cl	F	CH	C ₃₀ H ₃₁ ClFN ₅ O ₂
324642	(CH2)3CONHCH2CH2N(Me)2	H	Cl	F	CH	C ₂₈ H ₂₉ ClFN ₅ O ₂
324643	CH2CH2N(Me)2	H	F	CF3	CH	C ₂₈ H ₂₂ F ₄ N ₄ O
324644	(R)-3-(EtOCONH)-1-pyrrolidinyl-CH2CH2	Cl	Cl	H	CH	C ₂₉ H ₂₉ Cl ₂ N ₅ O ₃
324645	(R)-3-OH-1-pyrrolidinyl-CH2CH2	H	F	CF3	CH	C ₂₇ H ₂₄ F ₄ N ₄ O ₂
324646	cyclobutyl-NHCH2CH2	Cl	Cl	H	CH	C ₂₈ H ₂₄ Cl ₂ N ₄ O
324648	1-cyclopentyl-4-Pip	Cl	Cl	H	N	C ₂₈ H ₂₈ Cl ₂ N ₅ O

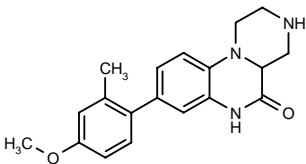
SOURCE – Schering-Plough.

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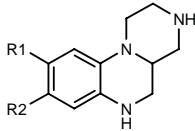
324913

8-(4-Methoxy-2-methylphenyl)-2,3,4,4a,5,6-hexahydro-1*H*-pyrazino[1,2-*a*]quinoxalin-5-one



C19 H21 N3 O2; Mol wt: 323.3939

ACTION – Modulator of 5-HT_{2A} and/or 5-HT_{2C} receptors, potentially useful for the treatment of obesity, schizophrenia and depression. Other exemplified substituted pyrazinoquinoxaline derivatives include the following:



Compound	R1	R2	Formula
324915	H	2-Me-4-MeO-Ph	C ₁₉ H ₂₃ N ₃ O
324916	H	2-CF ₃ -4-MeO-Ph	C ₁₉ H ₂₀ F ₃ N ₃ O
324918	H	2-Me-Ph	C ₁₈ H ₂₁ N ₃
324919	H	3-Me-Ph	C ₁₈ H ₂₁ N ₃
324920	H	4-Me-Ph	C ₁₈ H ₂₁ N ₃
324922	H	2-CF ₃ -4-F-Ph	C ₁₈ H ₁₇ F ₄ N ₃
324923	4-Me-Ph	H	C ₁₈ H ₂₁ N ₃

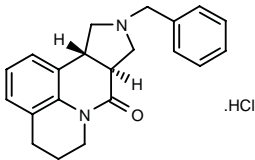
SOURCE – Bristol-Myers Squibb.

REFERENCES

1. Robichaud, A. et al. (Bristol-Myers Squibb Co.) *Substd. pyrazinoquinoxaline derivs. as serotonin receptor agonists and antagonists*. WO 0259127.

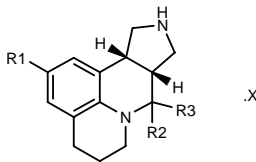
324924

(±)-*trans*-10-Benzyl-5,6,8,8a,9,10,11,11a-octahydro-4*H*-pyrido[3,2,1-*ij*]pyrrolo[3,4-*c*]quinolin-8-one hydrochloride



C₂₁ H₂₂ N₂ O . HCl; Mol wt: 354.8787

ACTION – Modulator of 5-HT_{2A} and/or 5-HT_{2C} receptors, potentially useful for the treatment of obesity, schizophrenia and depression. Other exemplified compounds include the following:



Compound	R1	R2	R3	X	Formula
324925	H	-O-		HCl	C ₁₄ H ₁₆ N ₂ O.HCl
324926	4-MeS-Ph	H	H	CF ₃ CO ₂ H	C ₂₁ H ₂₄ N ₂ S.C ₂ HF ₃ O ₂
324927	2-F-5-CF ₃ -PhNH	H	H	2CF ₃ CO ₂ H	C ₂₁ H ₂₁ F ₄ N ₃ .2C ₂ HF ₃ O ₂
324928	2-MeO-5-Me-PhNH	H	H	2CF ₃ CO ₂ H	C ₂₂ H ₂₇ N ₃ O.2C ₂ HF ₃ O ₂
324929	4-Me-1-Naph-NH	H	H	2CF ₃ CO ₂ H	C ₂₆ H ₂₇ N ₃ .2C ₂ HF ₃ O ₂
324930	2-F-6-CF ₃ -PhCH ₂ NH	H	H	2CF ₃ CO ₂ H	C ₂₂ H ₂₃ F ₄ N ₃ .2C ₂ HF ₃ O ₂
324931	NHCOPh	H	H	2CF ₃ CO ₂ H	C ₂₁ H ₂₃ N ₃ O.2C ₂ HF ₃ O ₂
324932	2,6-(Cl) ₂ -Ph	H	H	CF ₃ CO ₂ H	C ₂₀ H ₂₀ Cl ₂ N ₂ .C ₂ HF ₃ O ₂

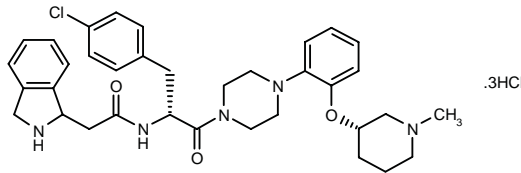
SOURCE – Bristol-Myers Squibb.

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1. Fevig, J.M. et al. (Bristol-Myers Squibb Co.) *Substd. pyrroloquinolines and pyridoquinolines as serotonin agonists and antagonists*. WO 0259124.

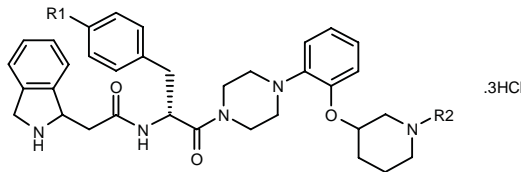
325026

N-[1(*R*)-(4-Chlorobenzyl)-2-[4-[2-[1-methylpiperidin-3(*S*)-yloxy]phenyl]piperazin-1-yl]-2-oxoethyl]-2-(2,3-dihydro-1*H*-isoindol-1-yl)acetamide trihydrochloride



C₃₅ H₄₂ Cl N₅ O₃ . 3HCl; Mol wt: 725.5845

ACTION – Melanocortin receptor agonist, considered to have potential for the treatment of obesity, diabetes and male and female sexual dysfunction. Other exemplified compounds are:



Compound	R1	R2	Isomer	Formula
325027	Cl	H	3R	C ₃₄ H ₄₀ ClN ₅ O ₃ .3HCl
325028	OMe	Me	3S	C ₃₆ H ₄₆ N ₅ O ₄ .3HCl

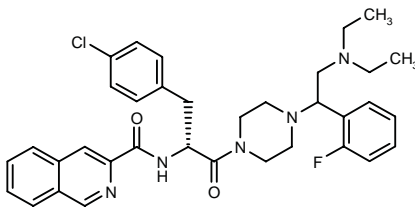
SOURCE – Lilly.

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1. Briner, K. et al. (Eli Lilly and Company) *Piperazine- and piperidine-derivs. as melanocortin receptor agonists*. WO 0259108, WO 0259117.

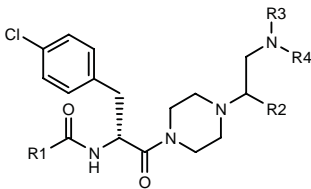
325030

N-[1(*R*)-(4-Chlorobenzyl)-2-[4-[2-(diethylamino)-1-(2-fluorophenyl)ethyl]piperazin-1-yl]-2-oxoethyl]isoquinoline-3-carboxamide



C₃₅ H₃₉ Cl F N₅ O₂; Mol wt: 616.1771

ACTION – Melanocortin receptor agonist, considered to have potential for the treatment of obesity, diabetes and male and female sexual dysfunction. Other exemplified compounds are:



Compound	R1	R2	R3	R4	Formula
325031	1,2,3,4-tetrahydro-3(R)-isoquinolinyl	2,4-(F)2-Ph	Et	Et	C ₃₅ H ₄₂ ClF ₂ N ₅ O ₂
325032	2,3-dihydro-1-isoindolyl-CH2	2-F-Ph	Et	Et	C ₃₅ H ₄₃ ClFN ₅ O ₂
325033	1,2,3,4-tetrahydro-3(R)-isoquinolinyl	4-CF3-Ph	Et	Et	C ₃₆ H ₄₃ ClF ₃ N ₅ O ₂
325034	2,3-dihydro-1-isoindolyl-CH2	cyclohexyl	SO2Me	Et	C ₃₄ H ₄₈ ClN ₅ O ₄ S
325035	2-Me-2,3-dihydro-1-isoindolyl-CH2	2-Cl-Ph	Et	Et	C ₃₆ H ₄₅ Cl ₂ N ₅ O ₂
325037	1-Me-2,3-dihydro-1-isoindolyl-CH2	2-F-Ph	Et	Et	C ₃₆ H ₄₅ ClFN ₅ O ₂
325038	1,2,3,4-tetrahydro-3(R)-isoquinolinyl	2-F-Ph	Ac	Me	C ₃₄ H ₃₆ ClFN ₅ O ₃
325039	2,3-dihydro-1-isoindolyl-CH2	cyclohexyl	SO2Me	H	C ₃₂ H ₄₄ ClN ₅ O ₄ S

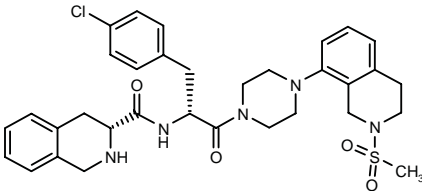
SOURCE – Lilly.

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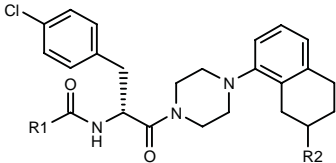
325041

N-[1(R)-(4-Chlorobenzyl)-2-[4-[2-(methylsulfonyl)-1,2,3,4-tetrahydroisoquinolin-8-yl]piperazin-1-yl]-2-oxoethyl]-1,2,3,4-tetrahydroisoquinoline-3(R)-carboxamide



C33 H38 Cl N5 O4 S; Mol wt: 636.2132

ACTION – Melanocortin receptor agonist, considered to have potential for the treatment of obesity, diabetes and male and female sexual dysfunction. Other exemplified compounds are:



Compound	R1	R2	*Isomer	Formula
325042	1,2,3,4-tetrahydro-3(R)-isoquinolinyl	N(Et)2	R	C ₃₇ H ₄₆ ClN ₅ O ₂
325044	1,1(Me)2-1,2,3,4-tetrahydro-3-isoquinolinyl	N(Et)2	R	C ₃₉ H ₅₀ ClN ₅ O ₂
325045	1,2,3,4-tetrahydro-1-isoquinolinyl-CH2	N(Et)2	R	C ₃₈ H ₄₈ ClN ₅ O ₂
325046	2,3-dihydro-1H-1-isoindolyl-CH2	1-pyrrolidinyl		C ₃₇ H ₄₄ ClN ₅ O ₂

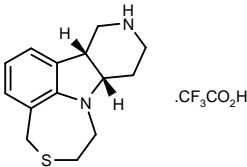
SOURCE – Lilly.

REFERENCES

1. Backer, R.T. et al. (Eli Lilly and Company) *Substd. piperidines/piperazines as melanocortin receptor agonists*. WO 0259107.

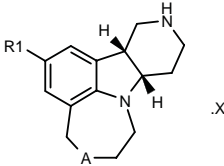
325193

(7bR,11aS)-2,4,7b,8,9,10,11,11a-Octahydro-1H-pyrido[4,3-b][1,4]thiazepino[6,5,4-h]indole trifluoroacetate



C14 H18 N2 S . C2 H F3 O2; Mol wt: 360.3981

ACTION – Modulator of 5-HT_{2A} and/or 5-HT_{2C} receptors, particularly useful for the treatment of obesity, schizophrenia and depression. Other exemplified substituted pyridoindoles include the following:



Compound	R1	A	X	Formula
325194	2-CF3-4-EtO-Ph	S	CF3CO2H	C ₂₃ H ₂₅ F ₃ N ₂ OSC ₂ HF ₃ O ₂
325195	2-CF3-4-MeO-Ph	O	CF3CO2H	C ₂₂ H ₂₃ F ₃ N ₂ O ₂ C ₂ HF ₃ O ₂
325197	2-Cl-5-CF3-PhNH	O	2CF3CO2H	C ₂₁ H ₂₁ ClF ₃ N ₃ O ₂ C ₂ HF ₃ O ₂
325198	2,5-(MeO)2-PhNH	O	2CF3CO2H	C ₂₂ H ₂₇ N ₃ O ₃ 2C ₂ HF ₃ O ₂
325199	2,5-(Me)2-PhNH	O	2CF3CO2H	C ₂₂ H ₂₇ N ₃ O ₂ 2C ₂ HF ₃ O ₂
325200	1,3-dioxo-2-isoindolyl	O	2CF3CO2H	C ₂₂ H ₂₁ N ₃ O ₃ 2C ₂ HF ₃ O ₂
325201	2,6-(F)2-PhCH2NH	O		C ₂₁ H ₂₃ F ₂ N ₃ O
325202	2-F-3-Cl-6-CF3-PhNH	S		C ₂₂ H ₂₂ ClF ₄ N ₃ S

SOURCE – Bristol-Myers Squibb.

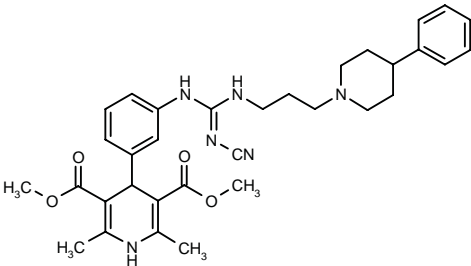
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BMS-214428

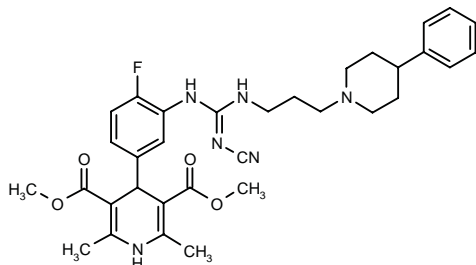
323883

4-[3-[N³-Cyano-N²-[3-(4-phenylpiperidin-1-yl)propyl]-guanidino]phenyl]-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylic acid dimethyl diester



C33 H40 N6 O4; Mol wt: 584.7170

ACTION – Potent neuropeptide Y (NPY) Y_1 receptor antagonist ($K_i = 0.079$ nM), with improved permeability properties in Caco-2 cells and enhanced oral bioavailability compared to the parent compound BMS-193885, but unable to penetrate the blood–brain barrier. Potentially useful for the treatment of obesity. Another related compound is:



BMS-224095 [323884]: C33 H39 F N6 O4

SOURCE – Bristol-Myers Squibb.

REFERENCES

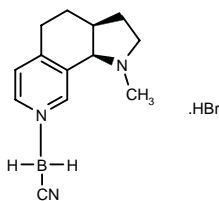
1. Poindexter, G.S. et al. (Bristol-Myers Squibb Co.) *Dihydropyridine NPY antagonists: Cyanoguanidine deriv.* US 6001836, WO 9854136.

2. Poindexter, G.S. et al. *Dihydropyridine neuropeptide Y Y_1 receptor antagonists: Cyanoguanidine-linked derivatives with improved oral bioavailability.* Drugs Fut 2002, 27(Suppl. A): Abst C74.

TREATMENT OF POISONING, DRUG ABUSE & DEPENDENCY

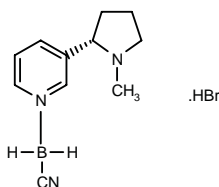
324625

(*T*-4)-(Cyano- κ C)(*cis*-1-methyl-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*h*]isoquinoline- κ N⁸]dihydroboron hydrobromide

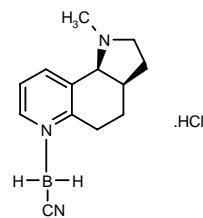


C13 H18 B N3. HBr; Mol wt: 308.0291

ACTION – Modulator of neuronal nicotinic acetylcholine $\alpha 7$ receptors that demonstrated partial agonist activity at nicotinic $\alpha 7$ receptors expressed in *Xenopus* oocytes, as measured in electrophysiological assays. Potentially useful for the treatment of nicotine, amphetamine, methamphetamine or cocaine abuse, as well as CNS disorders such as schizophrenia, Alzheimer's disease, Parkinson's disease, attention deficit disorder, depression and anxiety. Other exemplified boron-containing nicotine analogues are:



324627: C11 H16 B N3. HBr



324628: C13 H18 B N3 . HCl

SOURCE – University of Kentucky, Lexington, KY (US).

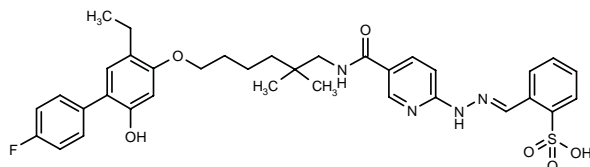
REFERENCES

1. Crooks, P.A. et al. (University of Kentucky) *Boron-containing nicotine analogs for use in the treatment of CNS pathologies.* WO 0257275.

DIAGNOSTIC AGENTS

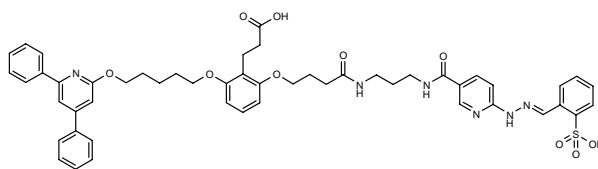
324265

2-[*N*-[5-[*N*-[6-(5-Ethyl-4'-fluoro-2-hydroxybiphenyl-4-yloxy)-2,2-dimethylhexyl]carbamoyl]pyridin-2-yl]-hydrazonomethyl]benzenesulfonic acid

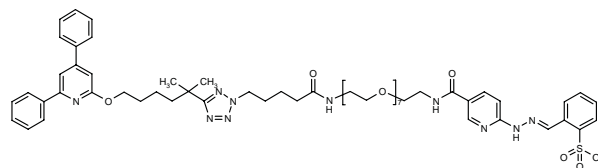


C35 H39 F N4 O6 S; Mol wt: 662.7791

ACTION – Reagent that is able to direct transformation to a radiopharmaceutical with binding affinity for the leukotriene LTB₄ receptor. A kit comprising this reagent, a reducing agent such as tin and ancillary ligands, particularly tricine and TPPTS, has been reported to be useful for imaging sites of infection and/or inflammation. This compound does not exhibit the adverse effects associated with radiolabeled proteins or antibodies. Other exemplified reagents include the following:

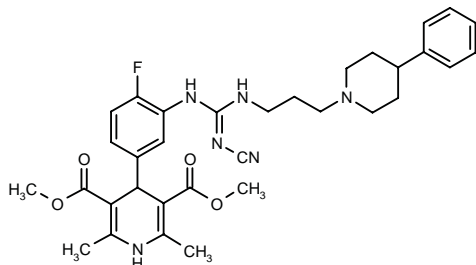


324267: C51 H54 N6 O10 S



324268: C59 H78 N10 O13 S

ACTION – Potent neuropeptide Y (NPY) Y_1 receptor antagonist ($K_i = 0.079$ nM), with improved permeability properties in Caco-2 cells and enhanced oral bioavailability compared to the parent compound BMS-193885, but unable to penetrate the blood–brain barrier. Potentially useful for the treatment of obesity. Another related compound is:



BMS-224095 [323884]: C33 H39 F N6 O4

SOURCE – Bristol-Myers Squibb.

REFERENCES

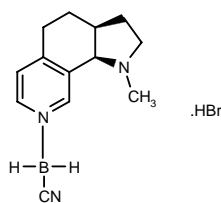
1. Poindexter, G.S. et al. (Bristol-Myers Squibb Co.) *Dihydropyridine NPY antagonists: Cyanoguanidine deriv.* US 6001836, WO 9854136.

2. Poindexter, G.S. et al. *Dihydropyridine neuropeptide Y Y_1 receptor antagonists: Cyanoguanidine-linked derivatives with improved oral bioavailability.* Drugs Fut 2002, 27(Suppl. A): Abst C74.

TREATMENT OF POISONING, DRUG ABUSE & DEPENDENCY

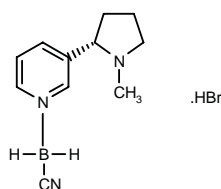
324625

(*T*-4)-(Cyano- κ C)(*cis*-1-methyl-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*h*]isoquinoline- κ N⁸]dihydroboron hydrobromide

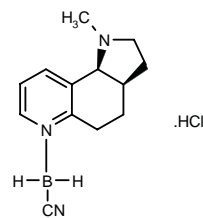


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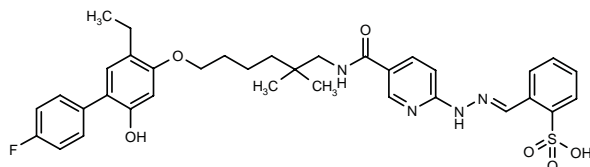
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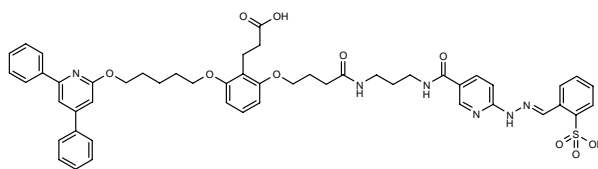
324265

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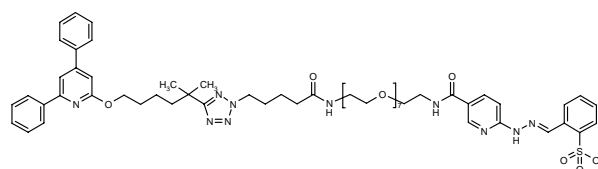


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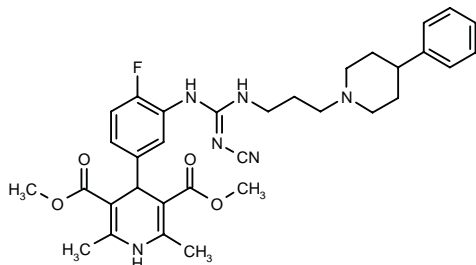


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SOURCE – Bristol-Myers Squibb.

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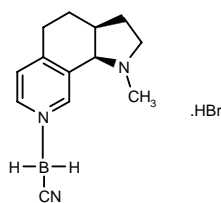
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TREATMENT OF POISONING, DRUG ABUSE & DEPENDENCY

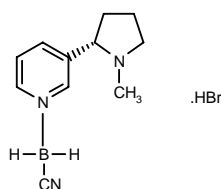
324625

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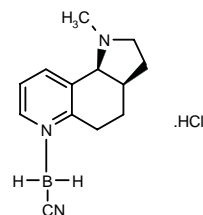


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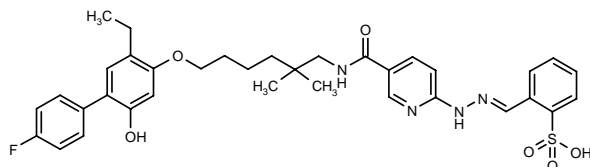
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DIAGNOSTIC AGENTS

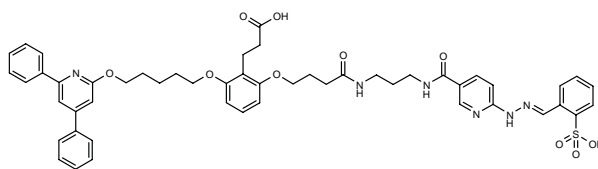
324265

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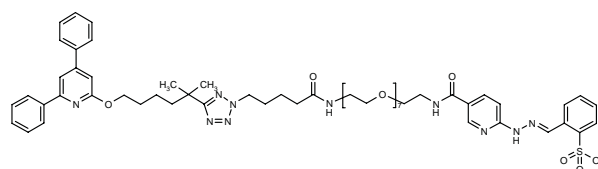


C35 H39 F N4 O6 S; Mol wt: 662.7791

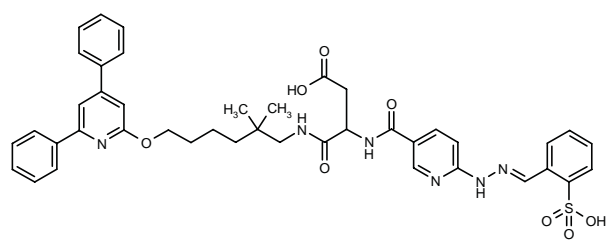
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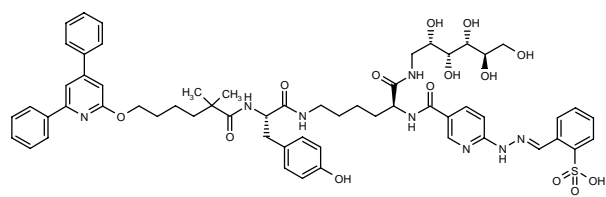
324267: C51 H54 N6 O10 S



324268: C59 H78 N10 O13 S



324269: C42 H44 N6 O8 S



324271: C59 H70 N8 O14 S

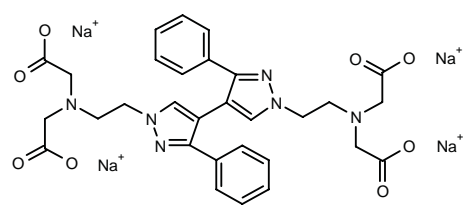
SOURCE – Bristol-Myers Squibb.

REFERENCES

1. Barrett, J.A. et al. (Bristol-Myers Squibb Co.) *Radiopharmaceutical for imaging infection and inflammation*. US 6416733.

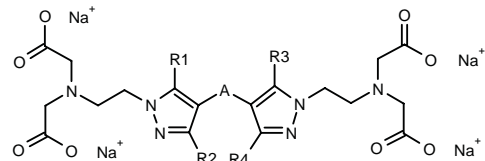
324990

2,2',2'',2'''-(3,3'-Diphenyl-1,1'-dihydro-4,4'-bipyrazol-1,1'-diyl)bis(ethylene)bis(nitrilo)tetrakis(acetic acid sodium salt)



C30 H28 N6 Na4 O8; Mol wt: 692.5452

ACTION – A ligand of transition metals such as gadolinium and dysprosium, reported to be useful as a magnetic resonance contrast agent. Other exemplified compounds are:



Compound	R1=R3	R2=R4	A	Formula
324991	Me	Me	bond	C ₂₂ H ₂₈ N ₆ Na ₄ O ₈
324992	H	4-NO ₂ -Ph	-CH ₂ -	C ₃₁ H ₂₈ N ₆ Na ₄ O ₁₂
325217	Me	Me	-CH ₂ -	C ₂₃ H ₃₀ N ₆ Na ₄ O ₈

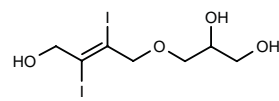
SOURCE – Rovi.

REFERENCES

1. Ballesteros García, P. and Cerdán García-Esteller, S. (Laboratorios Farmacéuticos Rovi SA) *Novel Gd(III) ligands with bi- and bis-azolic structures*. ES 2172461, WO 0259097.

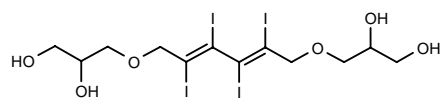
323095

3-(4-Hydroxy-2,3-diiodo-2-butenyloxy)propane-1,2-diol

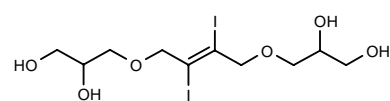


C7 H12 I2 O4; Mol wt: 413.9678

ACTION – X-ray contrast agent characterized by the absence of either electron-donating or -withdrawing substituents attached to the double bond and thus expected to be devoid of problems associated with the loss of iodide. Other specifically claimed iodinated alkenes are:



323096: C12 H18 I4 O6



323097: C10 H18 I2 O6

SOURCE – Amersham Health.

REFERENCES

1. Priebe, H. (Nycomed Imaging AS) *X-ray contrast agents*. US 6406680.

SYNTHETIC PORCINE SECRETIN

297091

L-Histidyl-L-seryl-L-aspartyl-glycyl-L-threonyl-L-phenylalanyl-L-threonyl-L-seryl-L-glutamyl-L-leucyl-L-seryl-L-arginyl-L-leucyl-L-arginyl-L-aspartyl-L-seryl-L-alanyl-L-arginyl-L-leucyl-L-glutamyl-L-arginyl-L-leucyl-L-leucyl-L-glutamyl-L-glycyl-L-leucyl-L-valinamide

C130 H220 N44 O41; Mol wt: 3055.4350

ACTION – Synthetic porcine secretin that stimulates pancreatic and gastric secretion.

INDICATION – For use as an aid in confirming the diagnosis of pancreatic dysfunction and the presence of gastrinoma that may become cancerous.

PRESENTATION – Lyophilized sterile powder in vials, containing 16 µg purified secretin.

PROPRIETARY NAME – *SecreFlo* (US).

SOURCES – Repligen; manufactured by Chesapeake Biological Laboratories, Baltimore, MD (US).

REFERENCES

1. *FDA approves SecreFlo for diagnosis of pancreatic dysfunction*. DailyDrugNews.com (Daily Essentials) 2002, April 9.

2. *FDA issues approvable letter for diagnostic secretin*. DailyDrugNews.com (Daily Essentials) 2000, May 31.

3. *FDA issues approvable letter for diagnostic secretin.* Repligen Corp. Press Release 2000, Dec 15.

4. *Repligen reports update on product development programs.* DailyDrugNews.com (Daily Essentials) 2000, Nov 29.

5. *Repligen updates product development programs.* DailyDrugNews.com (Daily Essentials) 2001, Feb 9.

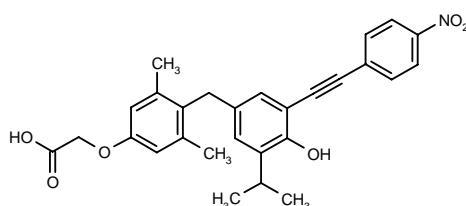
6. *Synthetic secretin available for diagnosing pancreatic dysfunction and gastrinoma.* DailyDrugNews.com (Daily Essentials) 2002, Sept 17.

PHARMACOLOGICAL TOOLS

NH-3

322549

2-[4-[4-Hydroxy-3-isopropyl-5-(4-nitrophenylethynyl)-benzyl]-3,5-dimethylphenoxy]acetic acid



C28 H27 N O6; Mol wt: 473.5223

ACTION – Thyroid hormone receptor (TR) antagonist ($K_i = 20$ and 93 nM at human $TR\beta_1$ and $TR\alpha_1$ receptors, respectively) that competitively blocks thyroid hormone (T_3)-induced transactivation in HeLa cells cotransfected with human $TR\beta_1$ and human $TR\alpha_1$ receptors ($IC_{50} = 0.37$ and 0.95 μ M, respectively). *In vivo*, compound inhibited T_3 -induced metamorphosis in *Xenopus laevis* and T_3 -induced target gene upregulation. It also prevented spontaneous metamorphosis induced by endogenous circulating thyroid hormones in *Xenopus laevis*. Potentially useful as a pharmacological tool for elucidating T_3 signaling and TR function.

SOURCE – University of California, San Francisco, CA (US).

REFERENCES

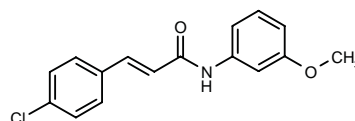
1. Lim, W. et al. *A thyroid hormone antagonist that inhibits thyroid hormone action in vivo.* J Biol Chem 2002, 277(38): 35664.

2. Nguyen, N.-H. et al. *Rational design and synthesis of a novel thyroid hormone antagonist that blocks coactivator recruitment.* J Med Chem 2002, 45(15): 3310.

SB-366791

323901

3-(4-Chlorophenyl)-N-(3-methoxyphenyl)-2-propenamide



C16 H14 Cl N O2; Mol wt: 287.7446

ACTION – Potent, selective and competitive vanilloid VR1 receptor antagonist proven to antagonize the capsaicin-induced increase in cytoplasmic calcium concentrations in human VR1-expressing cells ($pK_b = 7.6$, $pA_2 = 7.71$), to block the capsaicin-evoked inward current ($> 95\%$ at 1 μ M) and to inhibit the activation of VR1 receptors induced by heat and pH. Binding and electrophysiological experiments demonstrated no effect at NMDA, GABA, AMPA or Ca^{2+} -activated potassium channels, voltage-gated Na^+ , K^+ or Ca^{2+} channels, or a range of human receptors and enzymes. Potentially useful as a pharmacological tool for elucidating the physiopathological function of VR1 receptors.

SOURCE – GlaxoSmithKline.

REFERENCES

1. Rami, H.K. et al. *Identification of SB-366791, a potent and selective antagonist of vanilloid receptor-1.* Drugs Fut 2002, 27(Suppl. A): Abst P434.

3. *FDA issues approvable letter for diagnostic secretin.* Repligen Corp. Press Release 2000, Dec 15.

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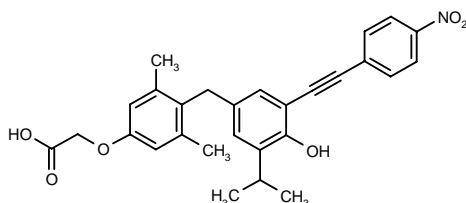
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SOURCE – University of California, San Francisco, CA (US).

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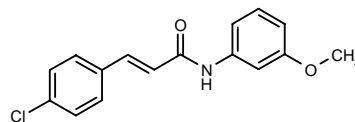
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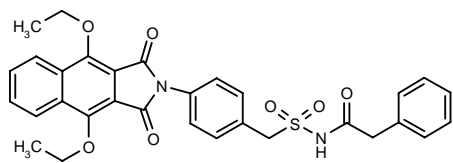
ANALGESIC AND ANESTHETIC
DRUGS

ANALGESIC DRUGS

323477

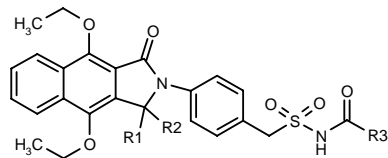
1-[4-(4,9-Diethoxy-1,3-dioxo-2,3-dihydro-1*H*-benzo[*f*]isindol-2-yl)phenyl]-*N*-(2-phenylacetyl)methanesulfonamide

N-[4-(4,9-Diethoxy-1,3-dioxo-2,3-dihydro-1*H*-benzo[*f*]isindol-2-yl)benzylsulfonyl]-2-phenylacetamide



C31 H28 N2 O7 S; Mol wt: 572.6352

ACTION – Prostanoid EP₄ receptor antagonist with potential in the treatment of pain, particularly neuropathic pain, as well as a broad range of PGE₂-mediated conditions including inflammation, immune diseases, erectile dysfunction, bone disorders, cardiovascular disorders, neurodegeneration, drug abuse, diabetic complications, renal dysfunction, etc. Other exemplified naphthalene derivatives are:



Compound	R1	R2	R3	Formula
323478	H	H	4-Me-PhCH ₂	C ₃₂ H ₃₂ N ₂ O ₆ S
323479	H	H	4-Ph-PhCH ₂	C ₃₇ H ₃₄ N ₂ O ₆ S
323480	H	H	4- <i>i</i> -Bu-PhCH(Me)	C ₃₆ H ₄₀ N ₂ O ₆ S
323482	H	H	1-Ph-cyclopropyl	C ₃₃ H ₃₂ N ₂ O ₆ S
323483	H	H	4-Me-5-thiazolyl-CH ₂	C ₂₉ H ₂₉ N ₃ O ₆ S ₂
323484		-O-	4-Cl-PhCH ₂	C ₃₁ H ₂₇ ClN ₂ O ₇ S
323485	H	H	4-(CF ₃ O)-PhCH ₂	C ₃₂ H ₂₉ F ₃ N ₂ O ₇ S
323486		-O-	1,3-benzodioxol-5-yl-CH ₂	C ₃₂ H ₂₈ N ₂ O ₉ S

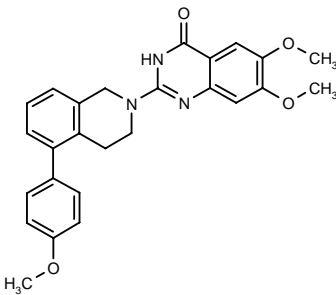
SOURCE – GlaxoSmithKline.

REFERENCES

1. Giblin, G.M.P. et al. (Glaxo Group Ltd.) *Naphthalene derivs. which bind to the EP4 receptor*. WO 0250032.

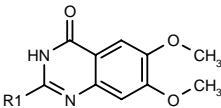
324122

6,7-Dimethoxy-2-[5-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinolin-2-yl]quinazolin-4(3*H*)-one

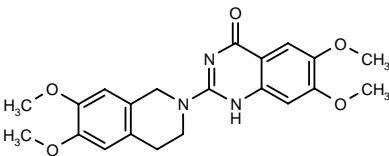


C26 H25 N3 O4; Mol wt: 443.5005

ACTION – Dual α_{1A} - and α_{1B} -adrenoceptor antagonist with pK_i values of 9.13 and 8.42, respectively, versus a pK_i value of 5.00 at α_{1D} -adrenoceptors. Potentially useful for the treatment of pain. Other exemplified quinazoline derivatives are:



Compound	R1	Formula
324124	2,3,4,9-tetrahydro-1H-pyrido[3,4- <i>b</i>]indol-2-yl	C ₂₁ H ₂₆ N ₄ O ₃
324125	1-Ph-4,5,6,7-tetrahydro-1H-imidazo[4,5- <i>c</i>]pyridin-5-yl	C ₂₂ H ₂₁ N ₅ O ₃



324123: C21 H23 N3 O5

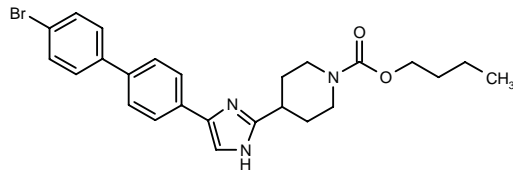
SOURCE – Roche.

REFERENCES

1. Becker, C.K. et al. (F. Hoffmann-La Roche AG) *Quinazoline derivs. as $\alpha_{1A/B}$ adrenergic receptor antagonists*. WO 0253558.

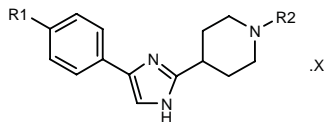
324126

4-[4-(4'-Bromobiphenyl-4-yl)-1*H*-imidazol-2-yl]piperidine-1-carboxylic acid butyl ester

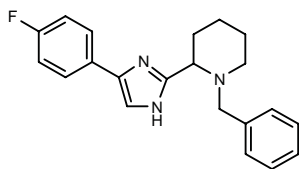


C25 H28 Br N3 O2; Mol wt: 482.4192

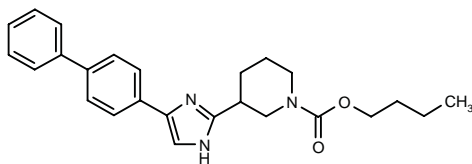
ACTION – Sodium channel modulator, as demonstrated in rat cerebral cortex preparations, claimed for the treatment of pain and migraine. Other exemplified 2-piperidylimidazoles are:



Compound	R1	R2	X	Formula
324127	Ph	t-BuOCO		C ₂₅ H ₂₉ N ₃ O ₂
324128	Ph	H	HCl	C ₂₀ H ₂₁ N ₃ ·HCl
324129	Ph	CH2Ph		C ₂₇ H ₂₇ N ₃
324130	F	cyclohexyl-CH2		C ₂₁ H ₂₈ FN ₃
324131	Ph	CONHBu		C ₂₅ H ₃₀ N ₄ O
324132	Ph	CSNHBu		C ₂₅ H ₃₀ N ₄ S
324133	Ph	CO2Et		C ₂₃ H ₂₅ N ₃ O ₂
324134	Ph	COBu		C ₂₅ H ₂₉ N ₃ O
324136	Ph	C6H13		C ₂₆ H ₃₃ N ₃
324138	OMe	CO2Bu		C ₂₀ H ₂₇ N ₃ O ₃



324135: C21 H22 F N3



324137: C25 H29 N3 O2

SOURCE – SCRAS.

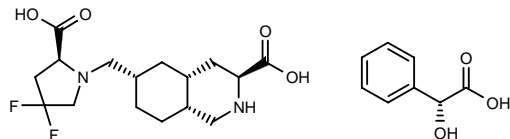
REFERENCES

1. Pommier, J. et al. (SCRAS [Société de Conseils de Recherches et d'Applications Scientifiques]) *Sodium channel modulators derived from 2-piperidylimidazoles*. FR 2818978, WO 0253559.

324139

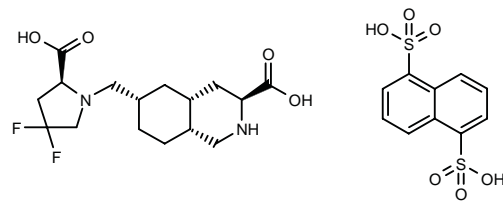
1-[(3*S*,4*aR*,6*S*,8*aR*)-3-Carboxyperhydroisoquinolin-6-ylmethyl]-4,4-difluoropyrrolidine-2(*S*)-carboxylic acid D-(–)-mandelic acid salt

6-[2(*S*)-Carboxy-4,4-difluoropyrrolidin-1-methyl]-(3*S*,4*aR*,6*S*,8*aR*)-perhydroisoquinoline-3-carboxylic acid mandelic acid salt



C16 H24 F2 N2 O4 . C8 H8 O3; Mol wt: 498.5198

ACTION – Selective antagonist of ionotropic glutamate GluR5 receptors, with potential for the treatment of neurological and neurodegenerative disorders, particularly pain and migraine. Another specifically claimed compound is:



324140: C16 H24 F2 N2 O4 . C10 H8 O6 S2

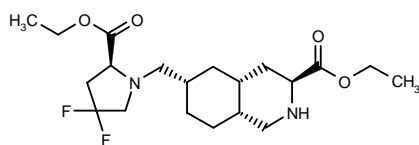
SOURCE – Lilly.

REFERENCES

1. Khau, V.V. et al. (Eli Lilly and Company) *Excitatory amino acid receptor antagonists*. WO 0253561.

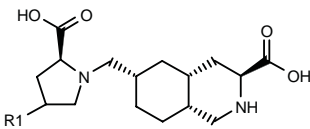
324189

(3*S*,4*aR*,6*S*,8*aR*)-6-[2(*S*)-(Ethoxycarbonyl)-4,4-difluoropyrrolidin-1-ylmethyl]perhydroisoquinoline-3-carboxylic acid ethyl ester

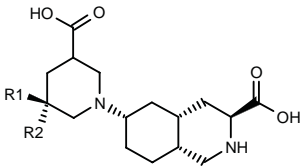


C20 H32 F2 N2 O4; Mol wt: 402.4788

ACTION – Selective ionotropic glutamate GluR5 receptor antagonist with potential for the treatment of neurological and neurodegenerative disorders, particularly pain and migraine. Other exemplified compounds include the following:



Compound	R1	Isomer	Formula
324191	F	S	C ₁₇ H ₂₇ FN ₂ O ₄
324193	2-Me-5-tetrazolyl-S	S	C ₁₉ H ₃₀ N ₆ O ₄ S
324194	SCH ₂ CO ₂ H	S	C ₁₉ H ₃₀ N ₂ O ₆ S
324201	OH	R	C ₁₇ H ₂₈ N ₂ O ₅



Compound	R1	R2	Isomer	Formula
324196	H	OH	S	C ₁₇ H ₂₈ N ₂ O ₅
324197	H	F	R	C ₁₇ H ₂₇ FN ₂ O ₄
324199	5-Ph-2-tetrazolyl	H	S	C ₂₄ H ₃₂ N ₆ O ₄
324200	H	5-Pr-2-tetrazolyl	R	C ₂₁ H ₃₄ N ₆ O ₄

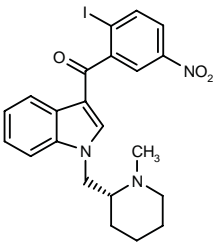
SOURCE – Lilly.

REFERENCES

1. Filla, S.A. et al. (Eli Lilly and Company) *Excitatory amino acid receptor antagonists*. WO 0253555.

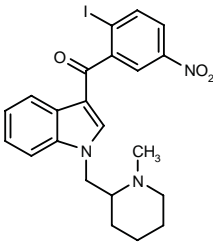
325447

1-(2-Iodo-5-nitrophenyl)-1-[1-[1-methylpiperidin-2(R)-ylmethyl]-1H-indol-3-yl]methanone



C22 H22 I N3 O3; Mol wt: 503.3338

ACTION – Agent with selective affinity for cannabinoid CB₂ receptors (K_i = 285 and 0.53 nM, respectively, at CB₁ and CB₂ receptors in binding assays), potentially useful for the treatment of pain, glaucoma, epilepsy and nausea, among other cannabinoid-associated disorders. Other exemplified aminoalkylindoles are:



Compound	Isomer	Formula
325448		C ₂₂ H ₂₂ IN ₃ O ₃
325449	S	C ₂₂ H ₂₂ IN ₃ O ₃

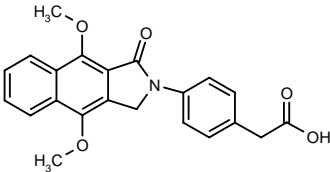
SOURCE – University of Connecticut, Storrs, CT (US).

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1. Makriyannis, A. and Deng, H. (University of Connecticut) *Receptor selective cannabimimetic aminoalkylindoles*. WO 0260447.

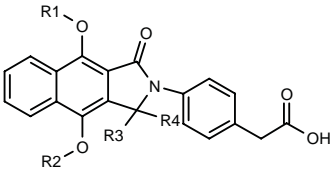
325995

2-[4-(4,9-Dimethoxy-1-oxo-2,3-dihydro-1H-benzo[f]isoindol-2-yl)phenyl]acetic acid



C22 H19 N O5; Mol wt: 377.3941

ACTION – Prostanoid EP₄ receptor ligand (pK_i > 6.0 for human EP₄ receptors in a scintillation proximity assay), with potential utility in the treatment of a broad range of disorders, particularly neuropathic pain. Other applications include inflammation, immune disorders, diuresis, erectile dysfunction, abnormal platelet function, bone diseases, cardiovascular diseases, neurodegenerative disorders, drug abuse, diabetic complications and kidney dysfunction. Other exemplified benzo[f]isoindole derivatives are:



Compound	R1	R2	R3	R4	Formula
325996	i-Pr	i-Pr	H	H	C ₂₆ H ₂₇ NO ₅
326012	Pr	Pr	H	H	C ₂₆ H ₂₇ NO ₅
326013	i-Pr	Et	H	H	C ₂₅ H ₂₅ NO ₅
326014	Et	i-Pr	H	H	C ₂₅ H ₂₅ NO ₅
326015	i-Pr	Pr	H	H	C ₂₆ H ₂₇ NO ₅
326016	Pr	i-Pr	H	H	C ₂₆ H ₂₇ NO ₅
326017	Et	Et	-O-		C ₂₄ H ₂₁ NO ₆
326018	i-Pr	i-Pr	-O-		C ₂₆ H ₂₅ NO ₆
326019	Pr	Pr	-O-		C ₂₆ H ₂₅ NO ₆
326020	i-Pr	Et	-O-		C ₂₅ H ₂₃ NO ₆

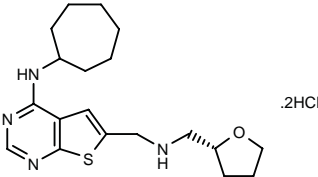
SOURCE – GlaxoSmithKline.

REFERENCES

1. Congreve, M.S. et al. (Glaxo Group Ltd.) *Benzo[f]isoindole derivs. with affinity to the EP4 receptor*. WO 0264564.

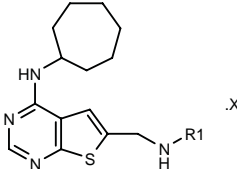
326248

N-Cycloheptyl-6-[tetrahydrofuran-2(*R*)-ylmethylamino-methyl]thieno[2,3-*d*]pyrimidin-4-amine dihydrochloride



C19 H28 N4 O S . 2HCl; Mol wt: 433.4450

ACTION – Agent with affinity for metabotropic glutamate mGluR₁ (mglu₁) receptors (IC₅₀ = 10 nM at mGluR₁ receptors from rat brain preparations), proven active in animal models of neuropathic pain at oral doses of 10 mg/kg. Potentially useful for the treatment of epilepsy, pain (including migraine and neuropathic pain), benzodiazepine withdrawal symptoms, Parkinson’s disease, anxiety and cerebral infarction. Other exemplified thieno[2,3-*d*]pyrimidine derivatives are:



Compound	R1	X	Formula
326249	3(S)-furyl	2HCl	C18H26N4OS.2HCl
326250	3-isoxazolyl	HCl	C17H21N5OS.HCl
326251	3-oxetanyl	fumarate	C17H24N4OS.C4H4O4
326252	3-thietanyl	2HCl	C17H24N4S2.2HCl

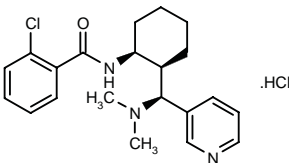
SOURCE – Yamanouchi.

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1. Itahana, H. et al. (Yamanouchi Pharmaceutical Co., Ltd.) *Thienopyrimidine deriv.* WO 0262803.

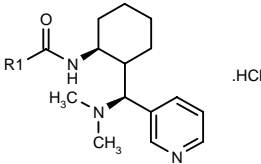
326320

2-Chloro-*N*-[(1*R*^{*},2*S*^{*})-2-[1(*R*^{*})-(dimethylamino)-1-(3-pyridyl)methyl]cyclohexyl]benzamide hydrochloride



C21 H26 Cl N3 O . HCl; Mol wt: 408.3703

ACTION – Agent with potential in the treatment of pain, urinary incontinence, pruritus, tinnitus aurium and diarrhea, found to suppress phenylquinone-induced writhing by 85% following i.v. administration to mice at a dose of 10 mg/kg. Other exemplified substituted propane-1,3-diamine derivatives are:



Compound	R1	Isomer	Formula
326321	Ph	S*	C21H27N3O.HCl
326322	2-F-Ph	S*	C21H26FN3O.HCl
326323	2-Me-Ph	S*	C22H29N3O.HCl
326324	Ph	R*	C21H27N3O.HCl
326325	2-F-Ph	R*	C21H26FN3O.HCl
326326	2-Cl-Ph	R*	C21H26ClN3O.HCl
326327	2-Me-Ph	R*	C22H29N3O.HCl
326329	Me	S*	C16H25N3O.HCl
326330	Me	R*	C16H25N3O.HCl

SOURCE – Grünenthal.

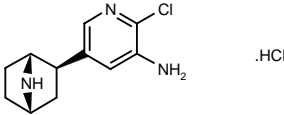
REFERENCES

1. Sundermann, B. et al. (Grünenthal GmbH) *Substd. propane-1,3-diamine derivs. and the pharmaceutical use thereof*. DE 10108307, WO 0266432.

RTI-7527-33

326285

exo-5-(7-Azabicyclo[2.2.1]hept-2-yl)-2-chloropyridin-3-amine hydrochloride



C11 H14 Cl N3 . HCl; Mol wt: 260.1665

ACTION – Analogue of epibatidine with high affinity for the nicotinic acetylcholine receptor (nAChR) αβ subtype (K_i = 0.001 nM) and excellent selectivity versus the αγ subtype (K_i = 13.9 nM). It exhibited potent functional antagonist activity at nAChRs in mice, as demonstrated by its ability to antagonize the antinociceptive effects of nicotine in the tail-flick and hot-plate tests (ED₅₀ = 0.00003 and 0.0006 mg/kg s.c., respectively), as well as in the hypothermia test (ED₅₀ = 0.017 mg/kg s.c.). Compound also produced agonist effects at higher doses, inducing antinociception in the tail-flick and hot-plate tests with ED₅₀ values of 0.02 mg/kg s.c.

SOURCE – Research Triangle Institute, Research Triangle Park, NC (US).

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1. Carroll, F.I. (Research Triangle Institute) *Cpds. and methods for promoting smoking cessation*. WO 0237927.

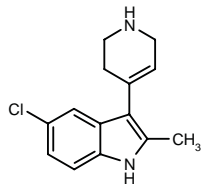
2. Carroll, F.I. et al. *Synthesis, nicotinic acetylcholine receptor binding, and antinociceptive properties of 2-exo-2-(2',3'-disubstituted 5'-pyridinyl)-7-azabicyclo-[2.2.1]heptanes: Epibatidine analogues*. J Med Chem 2002, 45(21): 4755.

PSYCHOPHARMACOLOGIC DRUGS

ANTIPSYCHOTIC DRUGS

324548

5-Chloro-2-methyl-3-(1,2,3,6-tetrahydropyridin-4-yl)-1 *H*-indole



C14 H15 Cl N2; Mol wt: 246.7395

ACTION – Potent and selective 5-HT₆ receptor agonist (IC₅₀ = 6 nM) with > 18-fold selectivity over 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{2A}, 5-HT_{2C}, 5-HT₄ and 5-HT₇ receptors and 6-fold selectivity over 5-HT_{3C} receptors. In functional *in vitro* studies, it exhibited full agonist activity with an EC₅₀ value of 0.6 nM. Potentially useful for the treatment of schizophrenia and depression.

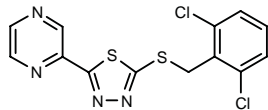
SOURCES – Carlsson Research; Merck KGaA.

REFERENCES

1. Mattsson, C. et al. *Novel, potent and selective 2-alkyl-3-(1,2,3,6-tetrahydropyridin-4-yl)-1H-indole as 5-HT₆ receptor agonists*. *Drugs Fut* 2002, 27(Suppl. A): Abst P369.

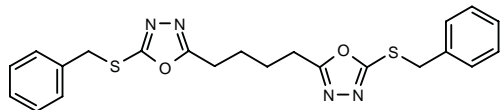
325865

2-[5-(2,6-Dichlorobenzylsulfanyl)-1,3,4-thiadiazol-2-yl]-pyrazine



C13 H8 Cl2 N4 S2; Mol wt: 355.2722

ACTION – Glycine transporter-2 (GlyT-2) inhibitor with potential in the treatment of CNS and muscle disorders, particularly psychosis, pain, epilepsy, neurodegenerative diseases, stroke, head trauma, multiple sclerosis, spasticity and myoclonus. Another exemplified heterocyclic compound is:



325866: C22 H22 N4 O2 S2

SOURCE – Telik.

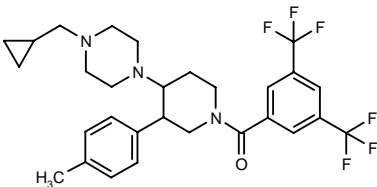
REFERENCES

1. Laborde, E. and Villar, H.O. (Telik, Inc.) *Heterocyclic inhibitors of glycine transporter -2*. WO 0264135.

TREATMENT OF MOOD DISORDERS

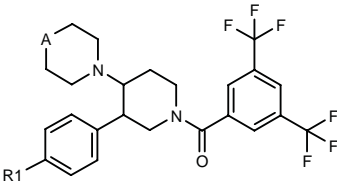
325592

(-)-1-[3,5-Bis(trifluoromethyl)phenyl]-1-[4-[4-(cyclopropylmethyl)piperazin-1-yl]-3-(4-methylphenyl)piperidin-1-yl]methanone



C29 H33 F6 N3 O; Mol wt: 553.5877

ACTION – Water-soluble tachykinin NK₁ receptor antagonist proven to inhibit [³H]-substance P binding to NK₁ receptors expressed in CHO cells with a pK_i of 9.28. Potentially useful for the treatment of depression and emesis, among other NK₁-related disorders. Other exemplified piperidine derivatives are:



Compound	R1	A	Isomer	Formula
325594	H	N(Me)	racemic,cis	C ₂₅ H ₂₇ F ₆ N ₃ O
325595	Cl	CH(OH)	racemic,cis	C ₂₅ H ₂₅ ClF ₆ N ₂ O ₂
325596	F	N(Me)	racemic,cis	C ₂₅ H ₂₆ F ₇ N ₃ O
325597	Me	N(Me)	(-)	C ₂₆ H ₂₉ F ₆ N ₃ O
325598	Cl	N(CH2-cyclopropyl)	(-)	C ₂₈ H ₃₀ ClF ₆ N ₃ O
325599	H	N(CH2-cyclopropyl)	(-)	C ₂₈ H ₃₁ F ₆ N ₃ O

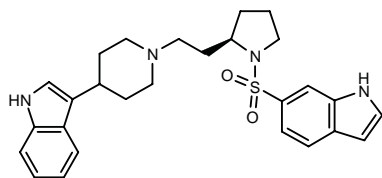
SOURCE – Roche.

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1. Kolczewski, S. et al. (F. Hoffmann-La Roche AG) *Piperidine derivs. as neurokinin 1 antagonists*. WO 0262784.

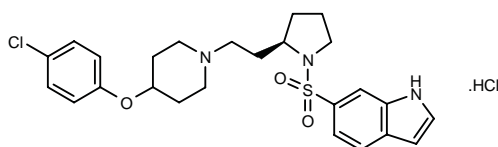
325600

3-[1-[2-[1-(1*H*-Indol-6-ylsulfonyl)pyrrolidin-2(*R*)-yl]ethyl]-piperidin-4-yl]-1*H*-indole



C27 H32 N4 O2 S; Mol wt: 476.6418

ACTION – 5-HT₇ receptor antagonist expected to be useful for the treatment of depression, migraine, anxiety, stroke, pain and sleep disorders. Another exemplified sulfonamide derivative is:



325602: C25 H30 Cl N3 O3 S . HCl

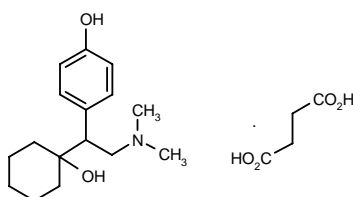
SOURCE – GlaxoSmithKline.

REFERENCES

1. Forbes, I.T. and Gribble, A.D. (SmithKline Beecham plc) *Sulfonamide cpds., their preparation and use*. WO 0262788.

326260

4-[2-(Dimethylamino)-1-(1-hydroxycyclohexyl)ethyl]-phenol succinate



C16 H25 N O2 . C4 H6 O4; Mol wt: 381.4659

ACTION – The succinate salt of *O*-desmethylvenlafaxine, a metabolite of venlafaxine endowed with 5-HT and noradrenaline reuptake-inhibitory activity. Reported to have improved solubility, permeability and bioavailability properties, and expected to be useful for the treatment of depression, panic disorders, anxiety, traumatic stress disorder, premenstrual dystrophic disorder, cognitive impairment, smoking cessation and hypothalamic amenorrhea, among other disorders. *O*-Desmethylvenlafaxine succinate was shown to be stable in rat jejunal fluids. According to rat jejunal perfusion results, predicted human *in vivo* Fa (fraction of dose absorbed) values of 61.3% (jejunal), 76.6% (ileum) and 16.4% (colon) were determined. Following oral administration to beagle dogs, complete absorption of *O*-desmethylvenlafaxine succinate was observed, and 121, 103 and 76% bioavailabilities were established for oral solution, capsule and tablet formulations, respectively.

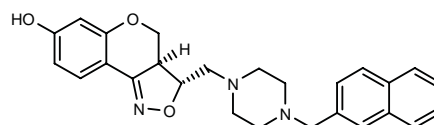
SOURCE – Wyeth.

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1. Hadfield, A.F. et al. (Wyeth) *Novel succinate salt of O-desmethyl-venlafaxine*. WO 0264543.

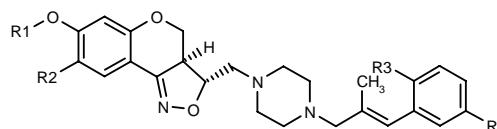
326474

cis-3-[4-(Naphthalen-2-ylmethyl)piperazin-1-ylmethyl]-3a,4-dihydro-3*H*-1-benzopyran[4,3-*c*]isoxazol-7-ol



C26 H27 N3 O3; Mol wt: 429.5173

ACTION – Antidepressant combining 5-HT reup-take-inhibitory and α_2 -adrenoceptor-antagonist activity. Compound gave pIC₅₀ values of 9.00, 8.26, 8.05 and 8.24, respectively, at human α_{2A} -, α_{2B} - and α_{2C} -adrenoceptors and the 5-HT transporter. Also potentially useful for the treatment of anxiety and eating disorders. Other exemplified isoxazoline derivatives are:



Compound	R1	R2	R3	R4	Formula
326479	Me	OMe	F	F	C ₂₇ H ₃₁ F ₂ N ₃ O ₄
326481	H	H	H	H	C ₂₆ H ₂₉ N ₃ O ₃
326483	CH ₂ CH ₂ OMe	H	H	H	C ₂₈ H ₃₅ N ₃ O ₄
326484	CH ₂ CH ₂ N(Me) ₂	H	H	H	C ₂₉ H ₃₈ N ₄ O ₃

SOURCE – Janssen.

REFERENCES

1. Andrés-Gil, J.I. et al. (Janssen Pharmaceutica NV) *Isoxazoline derivs. as anti-depressants*. WO 0266484.

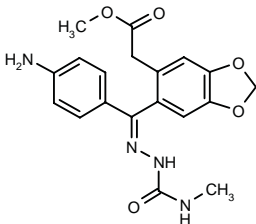
NEUROLOGIC DRUGS

ANTIEPILEPTIC DRUGS

325351

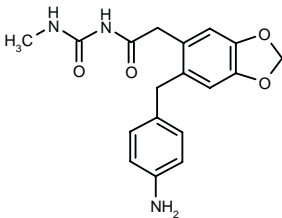
(Z)-2-[6-[1-(4-Aminophenyl)-1-(4-methylcarbazono)methyl]-1,3-benzodioxol-5-yl]acetic acid methyl ester

(Z)-1-(4-Aminophenyl)-1-[6-(methoxycarbonylmethyl)-1,3-benzodioxol-5-yl]methanone N-methylsemicarbazone



C19 H20 N4 O5; Mol wt: 384.3900

ACTION – Potent AMPA/kainate receptor antagonist able to reduce the kainic acid (KA)- and ATPA-evoked currents in cerebellar neurons (60 and 75% reduction, respectively, at 100 μ M) and protect against KA-induced neurotoxicity in cortical neurons (45% protection at 100 μ M). In mice, compound exhibited strong anticonvulsant activity against seizures induced by maximal electroshock and pentylene-tetrazol (ED_{50} = 15.7 and 14.7 μ mol/kg i.p., respectively), protected against audiogenic seizures (ED_{50} = 7.87 and 4.62 μ mol/kg i.p. against clonic and tonic phase, respectively) and both clonic and tonic seizures induced by i.c.v. AMPA (ED_{50} = 13.9 and 8.9 μ mol/kg i.p., respectively) or KA (ED_{50} = 16.6 μ mol/kg i.p.). Another related compound is:



325352: C18 H19 N3 O4

SOURCES – Università degli Studi di Catanzaro, Catanzaro (IT); Università degli Studi di Messina, Messina (IT); Università degli Studi di Milano, Milano (IT); Università degli Studi di Modena, Modena (IT); Università degli Studi di Pavia, Pavia (IT).

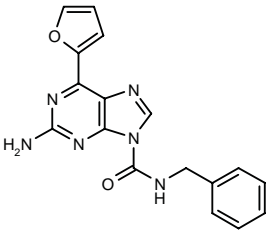
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TREATMENT OF EXTRAPYRAMIDAL MOVEMENT DISORDERS

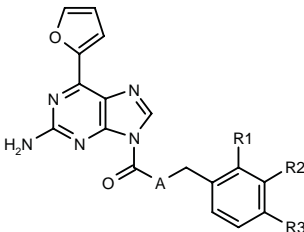
324338

2-Amino-N-benzyl-6-(2-furyl)-9H-purine-9-carboxamide



C17 H14 N6 O2; Mol wt: 334.3376

ACTION – Adenosine A_{2A} receptor antagonist (K_i = 1 nM) potentially useful for the treatment of movement disorders, particularly Parkinson's disease. Other exemplified purine derivatives are:



Compound	R1	R2	R3	A	Formula
324339	H	H	Me	NH	C ₁₈ H ₁₆ N ₆ O ₂
324340	Cl	H	H	NH	C ₁₇ H ₁₃ ClN ₆ O ₂
324341	H	Me	H	NH	C ₁₈ H ₁₆ N ₆ O ₂
324342	H	H	F	NH	C ₁₇ H ₁₃ FN ₆ O ₂
324343	H	H	H	O	C ₁₇ H ₁₃ N ₆ O ₃

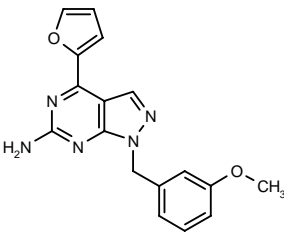
SOURCE – Vernalis Research.

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1. Gillespie, R.J. et al. (Vernalis Research Ltd.) Purine derivs. as purinergic receptor antagonists. WO 0255521.

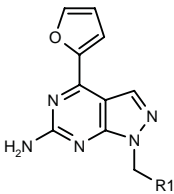
324344

4-(2-Furyl)-1-(3-methoxybenzyl)-1H-pyrazolo[3,4-d]-pyrimidin-6-amine



C17 H15 N5 O2; Mol wt: 321.3385

ACTION – Adenosine A_{2A} receptor antagonist (K_i = 2 nM), potentially useful for the treatment of movement disorders, particularly Parkinson’s disease. Other exemplified pyr-azolo[3,4-*d*]pyrimidine derivatives include the following:



Compound	R1	Formula
324345	2-F-Ph	C ₁₆ H ₁₂ FN ₅ O
324346	3-Me-Ph	C ₁₇ H ₁₅ N ₅ O
324347	2,6-(F)2-Ph	C ₁₆ H ₁₁ F ₂ N ₅ O
324348	CH2CH2Ph	C ₁₈ H ₁₇ N ₅ O

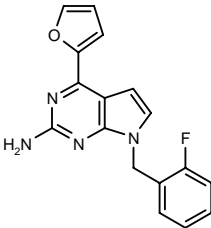
SOURCE – Vernalis Research.

REFERENCES

1. Gillespie, R.J. et al. (Vernalis Research Ltd.) *Pyr-azolo[3,4-d]pyrimidine derivs. and their use as purinergic receptor antagonists*. WO 0255082.

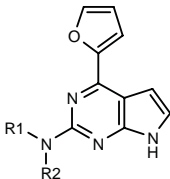
324349

7-(2-Fluorobenzyl)-4-(2-furyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-amine



C17 H13 F N4 O; Mol wt: 308.3147

ACTION – Adenosine A_{2A} receptor antagonist giving a K_i of 16 nM at A_{2A} receptors in radioligand binding assays. Potentially useful for the treatment of movement disorders, particularly Parkinson’s disease. Other exemplified pyrrolo[2,3-*d*]pyrimidines are:



Compound	R1	R2	Formula
324350	Me	Me	C ₁₂ H ₁₂ N ₄ O
324351	H	H	C ₁₀ H ₈ N ₄ O

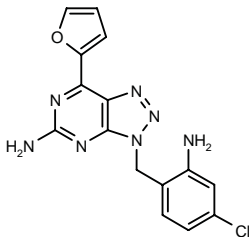
SOURCE – Vernalis Research.

REFERENCES

1. Gillespie, R.J. and Lerpiniere, J. (Vernalis Research Ltd.) *Pyrrolo[2,3-d]pyrimidine and their use as purinergic receptor antagonists*. WO 0255084.

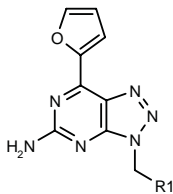
324352

3-(2-Amino-4-chlorobenzyl)-7-(2-furyl)-3*H*-[1,2,3]triazolo-[4,5-*d*]pyrimidin-5-amine



C15 H12 Cl N7 O; Mol wt: 341.7608

ACTION – Adenosine A_{2A} receptor antagonist (K_i = 1 nM) potentially useful for the treatment of movement disorders, particularly Parkinson’s disease. Other exemplified triazolo[4,5-*d*]pyrimidine derivatives are:



Compound	R1	Formula
324354	4-OH-2,6-(F)2-Ph	C ₁₅ H ₁₀ F ₂ N ₆ O ₂
324355	2-quinolyl	C ₁₈ H ₁₃ N ₇ O
324356	6-vinyl-2-Pyr	C ₁₆ H ₁₃ N ₇ O
324357	1,3-benzodioxol-5-yl	C ₁₆ H ₁₂ N ₆ O ₃

SOURCE – Vernalis Research.

REFERENCES

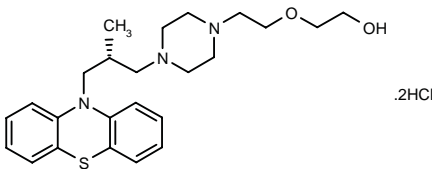
1. Gillespie, R.J. et al. (Vernalis Research Ltd.) *Triazolo[4,5-d]pyrimidine derivs. and their use as purinergic receptor antagonists*. WO 0255083.

TREATMENT OF NAUSEA AND VOMITING

(*R*)-DIXYRAZINE DIHYDROCHLORIDE

323304

2-[2-[4-[2(*R*)-Methyl-3-(10*H*-phenothiazin-10-yl)propyl]-piperazin-1-yl]ethoxy]ethanol dihydrochloride



C24 H33 N3 O2 S . 2HCl; Mol wt: 500.5315

ACTION – Antiemetic agent, the (*R*)-enantiomer of the known antipsychotic agent dixyrazine, particularly useful for preventing nausea and vomiting associated with cancer chemotherapy. In radioligand binding assays, compound exhibited affinity for dopamine D2 (pIC₅₀ = 8.6), D₃ (pIC₅₀ = 7.3) and D4.4 (pIC₅₀ = 6.8) receptors, and also for histamine H₁ receptors (pIC₅₀ = 9.7) and 5-HT₂ receptors (pIC₅₀ = 8.4). *In vivo*, (*R*)-dixyrazine dihydrochloride was able to prevent cisplatin-induced emesis in ferrets following a single oral dose of 60 mg/kg.

SOURCE – UCB.

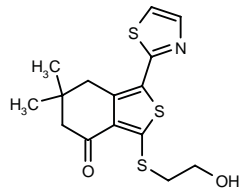
REFERENCES

1. Lamberty, Y. et al. (UCB SA) 2-[2-[4-[(2*R*)-2-Methyl-3-(10*H*-phenothiazin-10-yl)propyl]-1-piperazinyl]ethoxy]ethanol, process for the preparation thereof, pharmaceutical compsns. containing said cpd. and therapeutic uses thereof. WO 0250050.

TREATMENT OF COGNITION DISORDERS

316727

3-(2-Hydroxyethylsulfanyl)-6,6-dimethyl-1-(2-thiazolyl)-4,5,6,7-tetrahydro-2-benzothiophen-4-one



C15 H17 N O2 S3; Mol wt: 339.5023

ACTION – High-affinity GABA_A α5 receptor ligand (K_i = 1.6 nM) with good selectivity over α1, α2 and α3 subunits (K_i = 20,16 and 20 nM, respectively) and full inverse agonist activity at the α5β3γ2 receptor subtype. *In vivo*, a dose of 0.3 mg/kg i.p. significantly enhanced performance in the water maze task in rats. Potentially useful as a cognition-enhancing agent.

SOURCE – Merck Sharp & Dohme.

REFERENCES

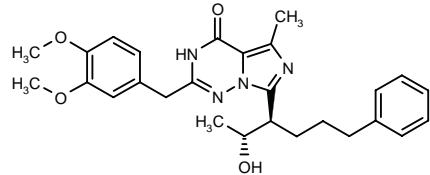
1. Broughton, H.B. et al. (Merck Sharp & Dohme Ltd.) *Thienylcyclohexanone derivs. as ligands of the GABA_A α₅ receptor subtype*. EP 0937072, JP 2001503408, US 6262103, WO 9818792.

2. Chambers, M.S. et al. *6,7-Dihydro-2-benzothiophen-4(5*H*)-ones: A novel class of GABA_A α₅ receptor inverse agonists*. J Med Chem 2002, 45(6): 1176.

3. Chambers, M.S. et al. *GABA_A α₅-subtype selective inverse agonists as potential cognition-enhancing agents*. Drugs Fut 2002, 27(Suppl. A): Abst P177.

323254

2-(3,4-Dimethoxybenzyl)-7-[1(*R*)-[1(*R*)-hydroxyethyl]-4-phenylbutyl]-5-methylimidazo[5,1-*f*][1,2,4]triazin-4(3*H*)-one



C27 H32 N4 O4; Mol wt: 476.5738

ACTION – Phosphodiesterase type 2 (PDE2) inhibitor that demonstrated *in vivo* activity in a rat memory test following oral administration at a dose of 1.0 mg/kg. Potentially useful for the treatment of perception, concentration, learning and memory disorders associated with dementia.

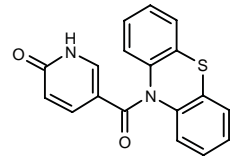
SOURCE – Bayer.

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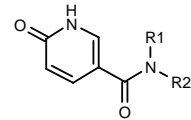
325886

5-(10*H*-Phenothiazin-10-ylcarbonyl)pyridin-2(1*H*)-one

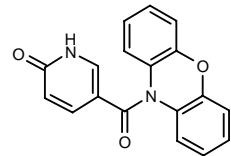


C18 H12 N2 O2 S; Mol wt: 320.3708

ACTION – Inhibitor of butyrylcholinesterase (BuChE; K_i = 42.9 μM) and acetylcholinesterase (AChE) with trypsin-activating effects. Potentially useful for the treatment of Alzheimer's disease. Other exemplified pyridones are:



Compound	R1	R2	Formula
325888	CH2Ph	CH2Ph	C ₂₀ H ₁₈ N ₂ O ₂
325889	i-Pr	i-Pr	C ₁₂ H ₁₈ N ₂ O ₂
325890	Et	Et	C ₁₀ H ₁₄ N ₂ O ₂
325894	-(CH2)4-		C ₁₀ H ₁₂ N ₂ O ₂
325895	-(CH2)5-		C ₁₁ H ₁₄ N ₂ O ₂



325897: C18 H12 N2 O3

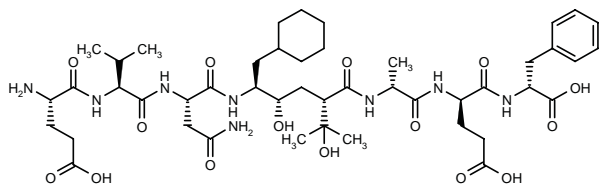
SOURCE – Dalhousie University, Halifax, NS (CA).

REFERENCES

1. Darvesh, S. et al. (Dalhousie University) *Pyridones and their use as modulators of serine hydrolase enzymes*. US 6436972.

326064

N-[(2S,4S,5S)-6-Cyclohexyl-5(S)-(L-glutamyl-L-valyl-L-asparaginylamino)-4(S)-hydroxy-2(S)-(1-hydroxy-1-methylethyl)hexanoyl]-D-alanyl-D-glutamyl-D-phenylalanine



C46 H72 N8 O15; Mol wt: 977.1158

ACTION – Peptide with the ability to inhibit β -amyloid cleavage enzyme (BACE, also known as transmembrane aspartyl protease β -secretase, β -site APP cleavage enzyme or memapsin-2), an enzyme implicated in the biosynthesis of β -amyloid peptide (A β). Potentially useful for the treatment of Alzheimer's disease, Down's syndrome, amyotrophic lateral sclerosis, stroke, head trauma, diabetes, pancreatitis, inclusion body myositis, prion disorders, Creutzfeldt-Jakob disease and progressive supranuclear palsy.

SOURCE – Pfizer.

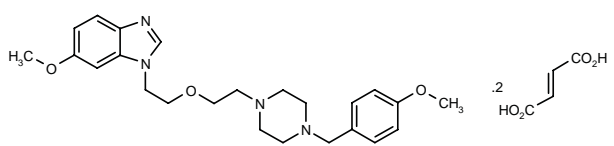
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TREATMENT OF Cerebrovascular Diseases

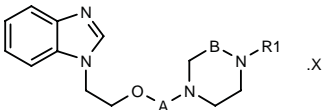
325238

6-Methoxy-1-[2-[2-[4-(4-methoxybenzyl)piperazin-1-yl]ethoxy]ethyl]-1H-benzimidazole difumarate



C24 H32 N4 O3 . 2 C4 H4 O4; Mol wt: 656.6850

ACTION – Agent with potential use in the treatment of cerebral ischemic disorders such as cerebral infarction, stroke and head injury. Compound reduced cerebral infarct area in rats subjected to middle cerebral artery occlusion by 30% following i.v. administration at a dose of 0.1 mg/kg. Other exemplified benzimidazole derivatives are:



Compound	A	B	R1	X	Formula
325239	-(CH2)2-	-CH2-	4-MeO-PhCH2	3HCl	C23H30N4O2.3HCl
325240	-(CH2)2-	-(CH2)2-	4-MeO-PhCH2	difumarate	C24H32N4O2.2C4H4O4
325241	-CH2-	-CH2-	2-MeO-Ph	oxalate	C21H26N4O2.C2H2O4

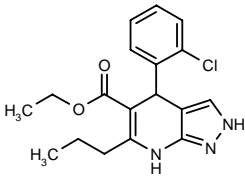
SOURCE – Toyama.

REFERENCES

1. Saito, A. et al. (Toyama Chemical Co., Ltd.) *Novel benzimidazole derivs. or their salts*. JP 2002193946.

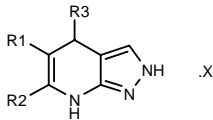
325605

4-(2-Chlorophenyl)-6-propyl-4,7-dihydro-2H-pyrazolo[3,4-b]pyridine-5-carboxylic acid ethyl ester



C18 H20 Cl N3 O2; Mol wt: 345.8280

ACTION – Glycogen synthase kinase-3 β (GSK-3 β) inhibitor (IC₅₀ = 25 nM) found to be active *in vivo* in a gerbil brain ischemia model. Potentially useful for the treatment of diabetes and complications related therewith, neurodegenerative disorders such as Alzheimer's disease, cerebral ischemia, Down's syndrome, progressive supranuclear paralysis, Parkinson's disease, Pick's disease, AIDS encephalopathy, Huntington's disease and manic-depressive psychosis, and also as an immunopotentiating agent. Other exemplified dihydropyrazolopyridine derivatives are:



Compound	R1	R2	R3	X	Isomer	Formula
325606	CO2Et	Me	2-Cl-Ph			C16H16ClN3O2
325607	CO2Et	CF3	2-Cl-Ph	maleate		C16H13ClF3N3O2.C4H4O4
325608	CO2Et	Pr	1-Naph			C22H23N3O2
325609	CN	Pr	2,1,3-benzoxadiazol-4-yl		R	C16H14N6O
325610	CO2Et	Pr	2-Cl-3-CF3-Ph			C19H19ClF3N3O2
325611	CN	Pr	2,1,3-benzoxadiazol-4-yl			C16H14N6O

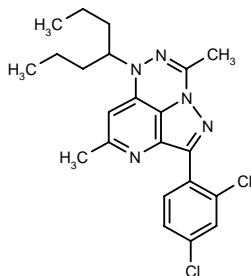
SOURCE – Mitsubishi Pharma.

REFERENCES

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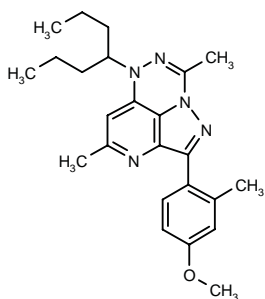
326151

2-(2,4-Dichlorophenyl)-4,8-dimethyl-6-(1-propylbutyl)-6H-1,3,6,7,8a-pentaazaacenaphthylene



C22 H25 Cl2 N5; Mol wt: 430.3805

ACTION – Corticotropin-releasing factor (CRF) receptor antagonist, expected to be useful for the treatment of stroke, depression, anxiety and irritable bowel syndrome. Another exemplified tricyclic compound is:



326152: C24 H31 N5 O

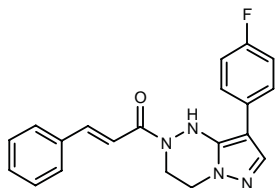
SOURCE – Neurocrine Biosciences.

REFERENCES

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FR-210575**327571**

8-(4-Fluorophenyl)-2-[3-phenyl-2(*E*)-propenoyl]-1,2,3,4-tetrahydropyrazolo[5,1-*c*][1,2,4]triazine



C20 H17 F N4 O; Mol wt: 348.3793

ACTION – Free radical scavenger with neuroprotective activity in cortical neurons *in vitro* and in a model of cerebral ischemia–reperfusion in rats. In cortical neurons, concentrations of 0.1–10 μ M protected against apoptosis induced by exposure to high oxygen or growth factor withdrawal. In rats with photothrombotic occlusion of the middle cerebral artery, i.v. infusion of 3.2 mg/kg/3 h significantly reduced the volume of focal cortical damage (35%) after 24 h. Potentially useful for the treatment of stroke.

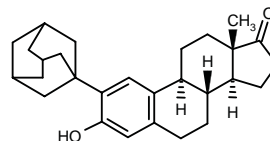
SOURCE – Fujisawa.

REFERENCES

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ZYC-3**314822**

2-(1-Adamantyl)-3-hydroxyestra-1,3,5(10)-trien-17-one



C28 H36 O2; Mol wt: 404.5904

ACTION – Non-receptor-binding estrogen analogue that was more effective than 17 β -estradiol in attenuating glutamate toxicity in HT-22 cells (EC_{50} = 0.16 and 1.90 μ M, respectively). In animals subjected to temporary middle cerebral artery occlusion and reperfusion, pretreatment with compound or 17 β -estradiol (100 μ g/kg i.v.) significantly reduced infarct volume compared to ovariectomy. Both estrogen analogues also significantly increased cerebral blood flow during occlusion in the nonischemic side only, and after reperfusion in both sides. Potentially useful for the treatment of stroke.

SOURCES – University of Florida, Gainesville, FL (US); University of North Texas, Fort Worth, TX (US); Washington University, St. Louis, MO (US).

REFERENCES

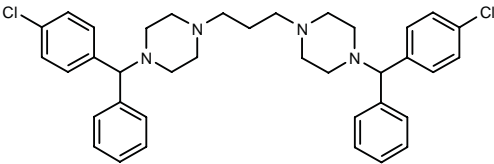
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3. Simpkins, J.W. et al. *Oestrogen receptor-independent mechanism for neuro-protection in stroke*. Br J Pharmacol 2002, 135(Suppl.): Abst 399P.
4. Yang, S.-H. et al. *Neuroprotective effects of a novel non-receptor binding estrogen analogue during stroke*. Stroke 2002, 33(1): Abst P199.

RESPIRATORY DRUGS

TREATMENT OF UPPER
RESPIRATORY TRACT DISORDERS

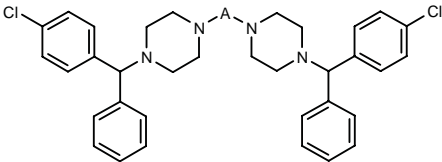
324774

1,1'-(1,3-Propylene)bis[4-[1-(4-chlorophenyl)-1-phenylmethyl]piperazine]

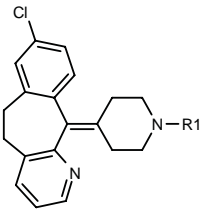


C37 H42 Cl2 N4; Mol wt: 613.6728

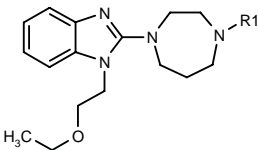
ACTION – Multibinding histamine H₁ antagonist with potential in the treatment of allergic rhinitis, urticaria, asthma and anaphylaxis. Other exemplified compounds are:



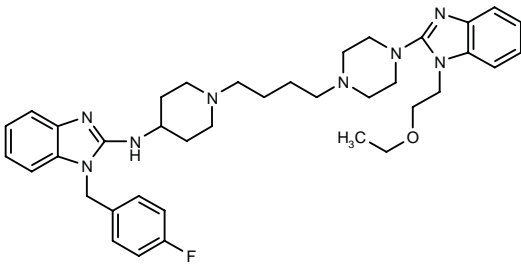
Compound	A	Formula
324775	CONH(CH ₂) ₄ NHCO-	C ₄₀ H ₄₆ Cl ₂ N ₆ O ₂
324776	-COCH ₂ OCH ₂ CO-	C ₃₈ H ₄₀ Cl ₂ N ₄ O ₃
324778	-CO ₂ (CH ₂) ₄ OCO	C ₄₀ H ₄₄ Cl ₂ N ₄ O ₄
324779	-CH ₂ CH ₂ OCH ₂ CONH(CH ₂) ₃ NHCOCH ₂ OCH ₂ CH ₂ -	C ₄₅ H ₅₆ Cl ₂ N ₆ O ₄



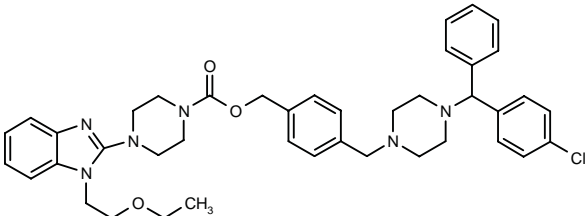
Compound	R1	Formula
324780	4-[4-Cl-PhCH(Ph)]-1-Piz-(CH ₂) ₃	C ₃₉ H ₄₂ Cl ₂ N ₄
324787	4-Cl-PhCH(Ph)	C ₃₂ H ₂₈ Cl ₂ N ₂



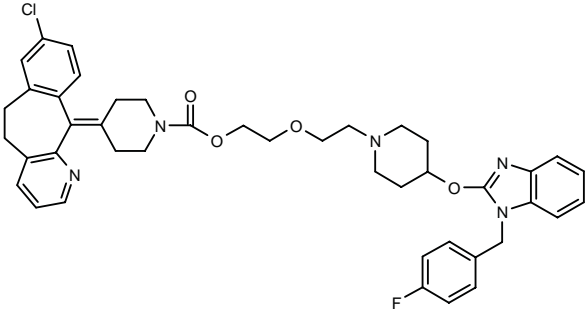
Compound	R1	Formula
324789	4-Cl-PhCH(Ph)	C ₂₉ H ₃₃ ClN ₄ O
324790	1-(EtOCH ₂ CH ₂)-2-benzimidazolyl	C ₂₇ H ₃₆ N ₆ O ₂



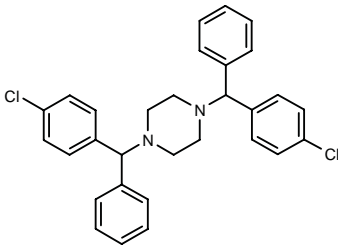
324781: C38 H49 F N8 O



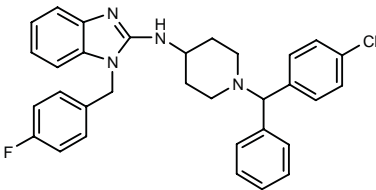
324783: C41 H47 Cl N6 O3



324785: C43 H45 Cl F N5 O4



324786: C30 H28 Cl2 N2



324788: C32 H30 Cl F N4

SOURCE – Theravance.

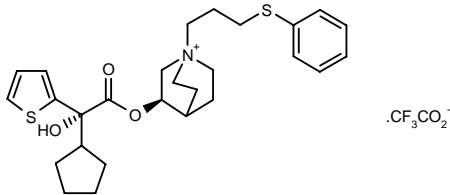
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ASTHMA THERAPY

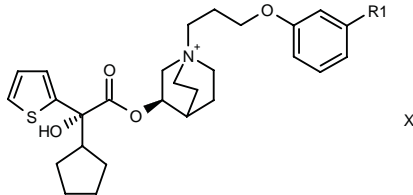
324170

3(R)-[2(S)-Cyclopentyl-2-hydroxy-2-(2-thienyl)acetoxyl]-1-[3-(phenylsulfanyl)propyl]-1-azoniabicyclo[2.2.2]octane trifluoroacetate



C29 H36 F3 N O5 S2; Mol wt: 599.7314

ACTION – Agent with antimuscarinic activity, with particularly high affinity for muscarinic M₃ receptors; it inhibited [³H]-NMS binding to human muscarinic receptors by 72.6 and 88.1% at concentrations of 10 and 100 nM, respectively. It is also reported to show bronchodilating activity and a long duration of action in a bronchospasm model in guinea pigs. Potentially useful for the treatment of respiratory, gastrointestinal or urinary diseases. Other exemplified quinuclidine derivatives are:



Compound	R1	X	Formula
324171	H	Br ⁻	C ₂₇ H ₃₆ BrNO ₄ S
324172	CN	CF ₃ CO ₂ ⁻	C ₃₀ H ₃₅ F ₃ N ₂ O ₆ S

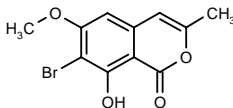
SOURCE – Almirall Prodesfarma.

REFERENCES

1. Prat Quinones, M. et al. (Almirall Prodesfarma, SA) *Novel quinuclidine derivs. and medicinal compsns. containing the same.* WO 0253564.

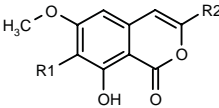
324413

7-Bromo-8-hydroxy-6-methoxy-3-methyl-1 H-2-benzopyran-1-one



C11 H9 Br O4; Mol wt: 285.0921

ACTION – Agent with tracheal smooth muscle relaxant activity shown to induce relaxation in pig tracheal smooth muscle preparations contracted with histamine (56 and 130%, respectively, at 10 and 100 μM). Potentially useful as a bronchodilator. Other exemplified compounds include the following:



Compound	R1	R2	Formula
324414	H	1-pyrrolidinyl-CH ₂	C ₁₅ H ₁₇ NO ₄
324415	H	1-Pip-CH ₂	C ₁₆ H ₁₉ NO ₄
324416	H	CH ₂ OAc	C ₁₃ H ₁₂ O ₆
324417	Ac	Me	C ₁₃ H ₁₂ O ₅

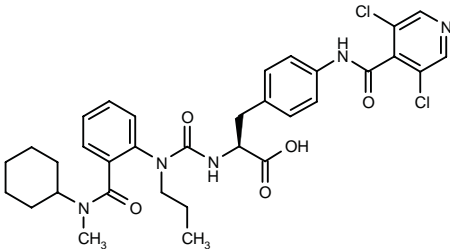
SOURCE – Mercian.

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1. Nakajima, T. et al. (Mercian Corp.) *Bronchodilator.* JP 2002161091.

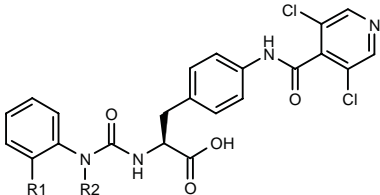
324706

N-[N-[2-(N-Cyclohexyl-N-methylcarbamoyl)phenyl]-N-propylcarbamoyl]-4-(3,5-dichloropyridin-4-ylcarbox-amido)-L-phenylalanine



C33 H37 Cl2 N5 O5; Mol wt: 654.5913

ACTION – Integrin α₄β₁ (VLA-4) and α₄β_{7b} integrin receptor antagonist (IC₅₀ < 100 nM), potentially useful for the treatment of immune and inflammatory disorders including multiple sclerosis, asthma, allergic rhinitis, allergic conjunctivitis, inflammatory lung disease, rheumatoid arthritis, polydermatomyositis, type 1 diabetes, transplant rejection, restenosis, viral infections, atopic dermatitis, myocarditis, inflammatory bowel disease, nephritis, psoriasis, cancer, atherosclerosis and cerebral ischemia. Other exemplified urea derivatives are:



Compound	R1	R2	Formula
324709	cyclohexyl-N(Me)CO	cyclopropyl-CH ₂	C ₃₄ H ₃₇ Cl ₂ N ₅ O ₅
324711	4-Me-1-Piz-SO ₂	H	C ₂₇ H ₂₈ Cl ₂ N ₆ O ₅ S

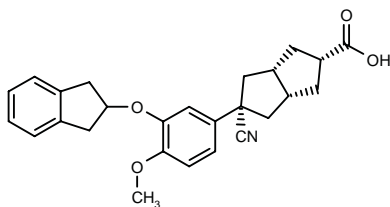
SOURCE – Almirall Prodesfarma.

REFERENCES

1. Jimenez Mayorga, J.M. et al. (Almirall Prodesfarma, SA) *Urea derivs. as integrin α₄ antagonists.* WO 0257242.

324772

(2*R**,3*aS**,5*S**,6*aR**)-5-Cyano-5-[3-(2,3-dihydro-1*H*-inden-2-yloxy)-4-methoxyphenyl]perhydropentalene-2-carboxylic acid



C26 H27 N O4; Mol wt: 417.5023

ACTION – Phosphodiesterase type 4 (PDE4) inhibitor (IC_{50} = 1.3 nM), potentially useful for the treatment of inflammatory conditions such as asthma, obstructive pulmonary disease, sepsis, nephritis and hepatitis, diabetes, allergic and autoimmune disorders, osteoporosis, obesity, depression, Parkinson's disease, ischemia–reperfusion injury and leukemia, among other PDE4-related diseases.

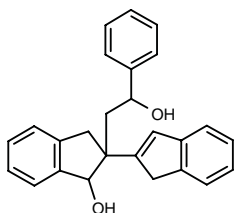
SOURCE – Ono.

REFERENCES

1. Nakai, H. and Kishikawa, K. (Ono Pharmaceutical Co., Ltd.) *Bicyclooctane derivs.* JP 2002193880.

325234

2-(2-Hydroxy-2-phenylethyl)-2,3-dihydro-1*H*,1'*H*-2,2'-biinden-1-ol



C26 H24 O2; Mol wt: 368.4736

ACTION – A representative compound from a series of indane derivatives that act as mast cell-stabilizing and antiinflammatory agents. It inhibited compound 48/80-stimulated histamine release from rat mast cells and was also able to inhibit arachidonic acid-induced ear edema formation following topical administration to mice (74% at a dose of 300 µg/ear). Potentially useful for the treatment of asthma, allergic rhinitis, allergic conjunctivitis, gout, rheumatic diseases, eczema, psoriasis and systemic lupus erythematosus. Further applications include hypertension and peripheral vascular diseases, disorders of the genitourinary tract, and also as an analgesic, antipyretic, local anesthetic, CNS depressant and hypoglycemic agent.

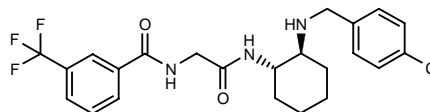
SOURCE – Venantius.

REFERENCES

1. Frankish, N. et al. (Venantius Ltd.) *Indane cpds. and their pharmaceutical use.* US 6433021.

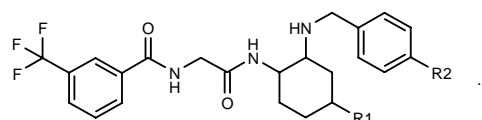
325307

N-[(1*S*,2*S*)-*N*-[2-(4-Chlorobenzylamino)cyclohexyl]-carbamoylmethyl]-3-(trifluoromethyl)benzamide

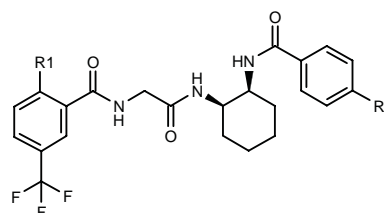


C23 H25 Cl F3 N3 O2; Mol wt: 467.9165

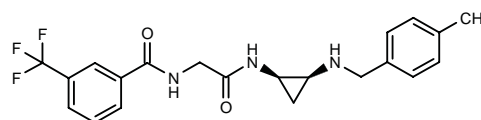
ACTION – Modulator of chemokine CCR2 receptors, expected to be useful for the treatment of asthma, rheumatoid arthritis, multiple sclerosis and atherosclerosis. Other exemplified compounds are:



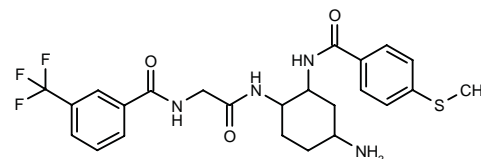
Compound	R1	R2	X	Isomer	Formula
325308	H	OCF3		cis	C ₂₄ H ₂₅ F ₆ N ₃ O ₃
325316	N(Me)2	Cl	CF3CO2H		C ₂₅ H ₃₀ ClF ₃ N ₄ O ₂ .C ₂ HF ₃ O ₂



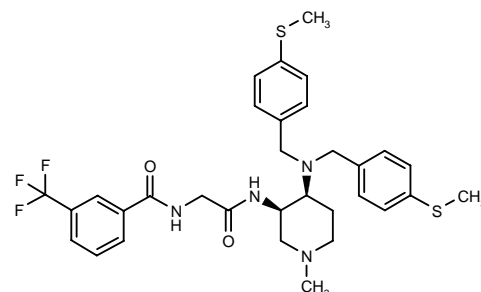
Compound	R1	R2	Formula
325309	H	OPh	C ₂₉ H ₂₈ F ₃ N ₃ O ₄
325311	NHCH2C(=CH2)Me	SO2NH2	C ₂₇ H ₃₂ F ₃ N ₅ O ₅ S
325312	i-PrNHCONH	SO2Me	C ₂₈ H ₃₄ F ₃ N ₅ O ₆ S
325313	i-ProCONH	SMe	C ₂₈ H ₃₃ F ₃ N ₄ O ₅ S



325310: C21 H22 F3 N3 O2



325314: C24 H27 F3 N4 O3 S



325315: C32 H37 F3 N4 O2 S2

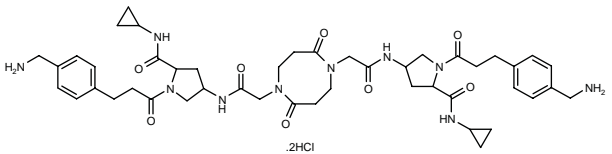
SOURCE – Bristol-Myers Squibb.

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1. Cherney, R. (Bristol-Myers Squibb Co.) *Cyclic derivs. as modulators of chemokine receptor activity*. WO 0260859.

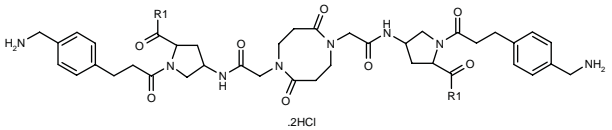
325476

4,4'-(2,6-Dioxoperhydro-1,5-diazocine-1,5-diyl)bis-(methylene)bis(carbonyl)bis(imino)bis[1-[3-[4-(amino-methyl)phenyl]propionyl]-N-cyclopropylpyrrolidine-2-carboxamide] dihydrochloride



C46 H62 N10 O8 . 2HCl; Mol wt: 955.9796

ACTION – Tryptase inhibitor (pK_i = 9.66) potentially useful for the treatment of inflammatory airways disorders such as bronchitis, bronchial asthma or chronic obstructive pulmonary disease. Other exemplified diazocine derivatives are:



Compound	R1	Formula
325477	OMe	C ₄₂ H ₅₆ N ₈ O ₁₀ .2HCl
325478	OCH2Ph	C ₅₄ H ₆₄ N ₈ O ₁₀ .2HCl
325480	OH	C ₄₀ H ₅₂ N ₈ O ₁₀ .2HCl
325482	NH2	C ₄₀ H ₅₄ N ₁₀ O ₈ .2HCl

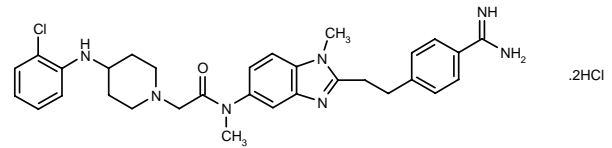
SOURCE – Altana Pharma.

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1. Bär, T. et al. (Byk Gulden Lomberg Chemische Fabrik GmbH) *Diazocine derivs. and their use as tryptase inhibitors*. WO 0260895.

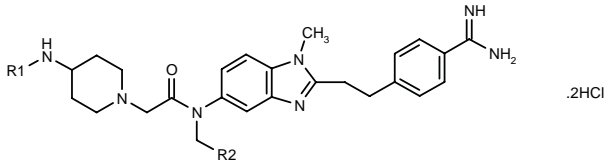
325793

N-[2-[2-(4-Amidinophenyl)ethyl]-1-methyl-1 H-benzimidazol-5-yl]-2-[4-(2-chlorophenylamino)piperidin-1-yl]-N-methylacetamide dihydrochloride



C31 H36 Cl N7 O . 2HCl; Mol wt: 631.0482

ACTION – Tryptase inhibitor (IC₅₀ < 0.0030 μM) with potential for the treatment of bronchial asthma, allergic rhinitis, allergic conjunctivitis, atopic dermatitis, urticaria, allergic otitis, allergic gastrointestinal disorders, Crohn's disease, ulcerative colitis, anaphylactic shock, septic shock, adult respiratory distress syndrome and arthritis. Other exemplified benzimidazole derivatives are:



Compound	R1	R2	Formula
325795	2-Pyr	1-Naph	C ₄₀ H ₄₂ N ₈ O.2HCl
325796	4-Cl-Ph	1-Naph	C ₄₁ H ₄₂ ClN ₇ O.2HCl
325797	2-Naph	1-Naph	C ₄₅ H ₄₅ N ₇ O.2HCl
325798	2-Naph	H	C ₃₅ H ₃₉ N ₇ O.2HCl
325799	2-I-Ph	H	C ₃₁ H ₃₆ IN ₇ O.2HCl

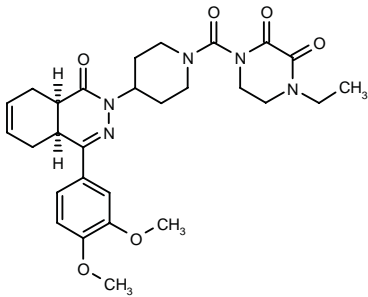
SOURCE – Boehringer Ingelheim.

REFERENCES

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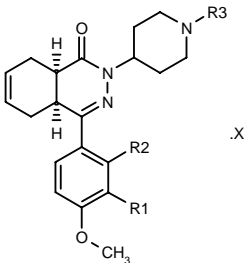
326215

1-[4-[(4a*S*,8a*R*)-4-(3,4-Dimethoxyphenyl)-1-oxo-1,2,4a,5,8,8a-hexahydrophthalazin-2-yl]piperidin-1-ylcarbonyl]-4-ethylpiperazine-2,3-dione



C28 H35 N5 O6; Mol wt: 537.6135

ACTION – Phosphodiesterase type 4 (PDE4) inhibitor (pIC₅₀ = 10.87), potentially useful for the treatment of acute and chronic inflammatory airways disorders such as bronchitis, allergic bronchitis, bronchial asthma, emphysema and chronic obstructive pulmonary disease. Other exemplified compounds are:

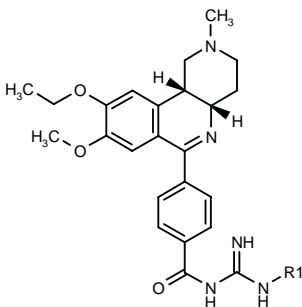


Compound	R1	R2	R3	X	Formula
326229	-OC(Me)2CH2-		t-BuNHCO		C ₂₉ H ₄₀ N ₄ O ₄
326230	OMe	H	4-Pyr-CH2		C ₂₇ H ₃₂ N ₄ O ₃
326231	OMe	H	thieno[2,3-d]pyrimidin-4-yl		C ₂₇ H ₂₉ N ₅ O ₃ S
326232	OMe	H	2-pyrimidinyl		C ₂₈ H ₂₉ N ₅ O ₃
326233	OMe	H	3-Pyr-CH2	2HCl	C ₂₇ H ₃₂ N ₄ O ₃ ·2HCl
326234	OMe	H	2-Pyr-CH2	2HCl	C ₂₇ H ₃₂ N ₄ O ₃ ·2HCl

SOURCE – Altana Pharma.

REFERENCES

1. Hatzelmann, A. et al. (Byk Gulden Lomberg Chemische Fabrik GmbH) *Phthalazinone-piperidino-derivs. as PDE4 inhibitors*. WO 0264584.



Compound	R1	Formula
326313	Pr	C ₂₇ H ₃₅ N ₅ O ₃
326315	cyclohexyl	C ₃₀ H ₃₉ N ₅ O ₃
326316	cyclohexyl-CH2	C ₃₁ H ₄₁ N ₅ O ₃
326317	Bu	C ₂₈ H ₃₇ N ₅ O ₃

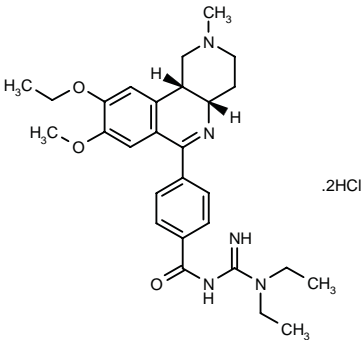
SOURCE – Altana Pharma.

REFERENCES

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326309

(+)-*cis*-*N*-[4-(9-Ethoxy-8-methoxy-2-methyl-1,2,3,4,4a,10b-hexahydrobenzo[*c*]-1,6-naphthyridin-6-yl)benzoyl]-*N*′, *N*′-diethylguanidine dihydrochloride

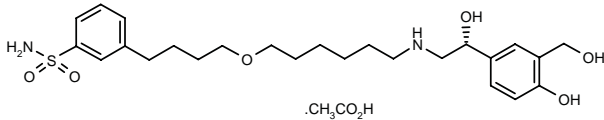


C28 H37 N5 O3 . 2HCl; Mol wt: 564.5541

ACTION – Phosphodiesterase type 3 (PDE3) and/or type 4 (PDE4) inhibitor (pIC₅₀ = 7.37 and 9.77, respectively), potentially useful for the treatment of respiratory disorders and dermatoses. Other exemplified 6-phenylbenzo[*c*]-1,6-naphthyridine derivatives are:

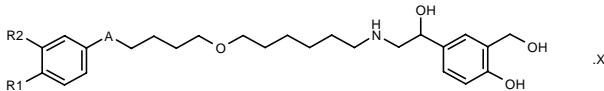
326335

3-[4-[6-[2(*R*)-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)-phenyl]ethylamino]hexyloxy]butyl]benzenesulfonamide acetate



C25 H38 N2 O6 S . C2 H4 O2; Mol wt: 554.7008

ACTION – β₂-Adrenoceptor agonist, potentially useful for the treatment of disorders associated with reversible airways obstruction such as asthma, chronic obstructive pulmonary disease, respiratory tract infection and rhinitis. Other exemplified phenethanolamine derivatives are:



Compound	R1	R2	A	X	Isomer	Formula
326336	H	4-morpholinyl-SO2	bond	acetate	R	C ₂₉ H ₄₄ N ₂ O ₇ S·C ₂ H ₄ O ₂
326337	H	CH2SO2NH2	bond		R	C ₂₆ H ₄₀ N ₂ O ₆ S
326338	H	SO2NH2	-CH2-		R	C ₂₆ H ₄₀ N ₂ O ₆ S
326342	CH2SO2-NH2	H	bond		R	C ₂₆ H ₄₀ N ₂ O ₆ S
326343	H	SO2NH2	bond	acetate	S	C ₂₅ H ₃₈ N ₂ O ₆ S·C ₂ H ₄ O ₂
326344	H	SO2NHCH2CH2-OCH2CH2OH	bond		R	C ₂₉ H ₄₆ N ₂ O ₆ S
326346	OMe	SO2NH2	bond	acetate	R	C ₂₆ H ₄₀ N ₂ O ₇ S·C ₂ H ₄ O ₂
326347	H	SO2NH2	bond		R	C ₂₅ H ₃₈ N ₂ O ₆ S

SOURCE – GlaxoSmithKline.

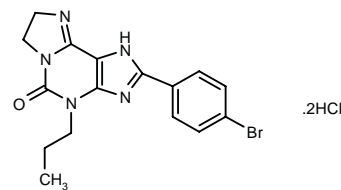
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1. Biggadike, K. et al. (Glaxo Group Ltd.) *Phenethanolamine derivs. for treatment of respiratory diseases*. WO 0266422.

KF-26777*

264440

2-(4-Bromophenyl)-4-propyl-4,5,7,8-tetrahydro-1*H*-imidazo[2,1-*i*]purin-5-one dihydrochloride



C16 H16 Br N5 O . 2HCl; Mol wt: 447.1622

ACTION – Potent adenosine A₃ receptor antagonist with subnanomolar affinity for human A₃ receptors (K_i = 0.20 nM) and high selectivity over A₁, A_{2A} and A_{2B} receptors (9,000-, 2,350- and 3,100-fold, respectively). It concentration-dependently inhibited Cl-IB-MECA-induced [³⁵S]-GTPγS binding to HEK293 cells (IC₅₀ = 270 nM) and enhanced intracellular Ca²⁺ concentration in HL-60 cells (K_B = 0.42 nM). Potentially useful for the treatment of brain ischemia and inflammatory diseases such as asthma.

SOURCE – Kyowa Hakko.

REFERENCES

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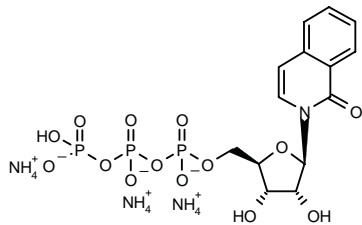
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*Identified compound **264440** Drug Data Rep 1998, 020(07): 0598.

TREATMENT OF CHRONIC
OBSTRUCTIVE PULMONARY DISEASE

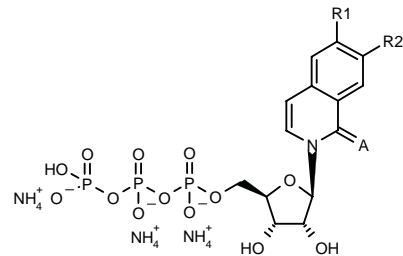
325778

Triphosphoric acid 1-deoxy-1-(1-oxo-1,2-dihydroisoquino-
lin-2-yl)-β-D-ribofuranos-5-yl ester triammonium salt

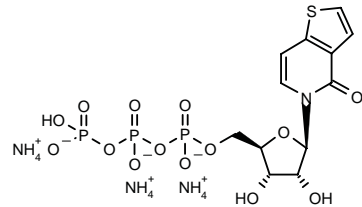


C14 H18 N O14 P3 . 3 H3 N; Mol wt: 568.3033

ACTION – Non-natural nucleotide P2Y, particularly P2Y₂, P2Y₄ and/or P2Y₆, receptor agonist. Potentially useful for the treatment of chronic obstructive pulmonary disease, chronic bronchitis, primary ciliary dyskinesia and cystic fibrosis, as well as disorders associated with inappropriate cellular glucose uptake. Other specifically claimed compounds are:



Compound	R1	R2	A	Formula
325780	H	Cl	O	C ₁₄ H ₁₇ ClNO ₁₄ P ₃ ·3H ₃ N
325781	H	CN	O	C ₁₅ H ₁₇ N ₂ O ₁₄ P ₃ ·3H ₃ N
325783	H	H	S	C ₁₄ H ₁₈ NO ₁₃ P ₃ ·3H ₃ N
325784	H	Cl	S	C ₁₄ H ₁₇ ClNO ₁₃ P ₃ ·3H ₃ N
325785	H	F	O	C ₁₄ H ₁₇ FNO ₁₄ P ₃ ·3H ₃ N
325786	H	F	S	C ₁₄ H ₁₇ FNO ₁₃ P ₃ ·3H ₃ N
325787	SMe	F	O	C ₁₅ H ₁₉ FNO ₁₄ P ₃ ·3H ₃ N
325788	N(Me) ₂	F	O	C ₁₆ H ₂₂ FN ₂ O ₁₄ P ₃ ·3H ₃ N
325790	OMe	F	O	C ₁₅ H ₁₉ FNO ₁₅ P ₃ ·3H ₃ N



325782: C12 H16 N O14 P3 S . 3 H3 N

SOURCE – Celltech Group.

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TREATMENT OF CYSTIC FIBROSIS

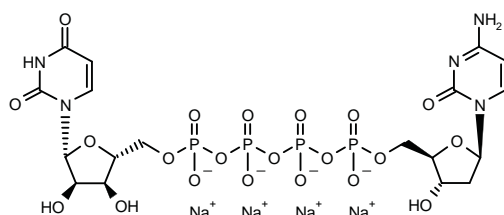
INS-37217

291491

*P*¹-(2'-Deoxycytidin-5'-yl)-*P*⁴-(uridin-5'-yl)tetrphosphate tetrasodium salt

Uridine 5'-(pentahydrogen tetraphosphate) P^{'''}→5'-ester with 2'-deoxycytidine tetrasodium salt

dCp4U



C18 H23 N5 Na4 O21 P4; Mol wt: 861.2497

ACTION – Agent for the treatment of cystic fibrosis (CF), a dinucleotide with full agonist activity at P2Y₂ and P2Y₄ receptors (EC₅₀ = 0.22 and 0.8 μM, respectively, for intracellular Ca²⁺ mobilization in astrocytoma cells expressing human receptors) and selectivity over P2Y₁ and P2Y₆ receptors. Compound stimulated chloride secretion in canine tracheal epithelium (EC₅₀ = 1.9 μM), mucin secretion from human airways cell cultures (EC₅₀ = 2.67 μM) and ciliary beat frequency in human airways explants (EC₅₀ = 8.3 μM). Compared to the natural P2Y agonist UTP, it was 50-fold more stable in the mucosal surface of the human nasal epithelium; in sputum samples obtained from CF patients, it was extremely stable, with a half-life of 25 h. Moreover, in sheep, nebulized compound provided a dose-dependent increase in tracheal mucus velocity, with a significant enhancement over 8 h after doses of 94 and 471 μmol. Currently in clinical evaluation in CF patients.

SOURCE – Inspire Pharmaceuticals.

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4. Crean, C.S. et al. *Dinucleoside tetraphosphates modified with lipophilic substituents: Selected structure-activity relationships at nucleotide G-protein coupled receptors*. 14th World Congr Pharmacol (July 7-12, San Francisco) 2002, Abst 146.16.
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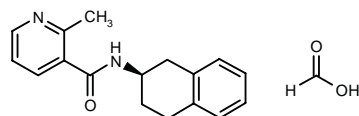
21. *Year 2000 at Genentech marked by significant progress on all fronts*. DailyDrugNews.com (Daily Essentials) 2001, Jan 23.

CARDIOVASCULAR DRUGS

TREATMENT OF DISORDERS OF THE CORONARY ARTERIES AND ATHEROSCLEROSIS

325974

2-Methyl-*N*-[1,2,3,4-tetrahydronaphthalen-2(*R*)-yl]pyridin-3-carboxamide formate



C17 H18 N2 O . C H2 O2; Mol wt: 312.3670

TREATMENT OF CYSTIC FIBROSIS

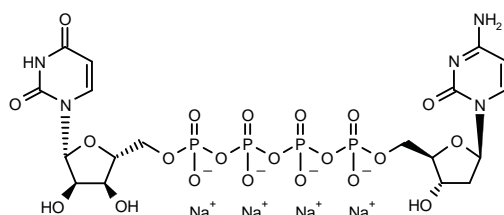
INS-37217

291491

*P*¹-(2'-Deoxycytidin-5'-yl)-*P*⁴-(uridin-5'-yl)tetrphosphate tetrasodium salt

Uridine 5'-(pentahydrogen tetraphosphate) P^{'''}→5'-ester with 2'-deoxycytidine tetrasodium salt

dCp4U



C18 H23 N5 Na4 O21 P4; Mol wt: 861.2497

ACTION – Agent for the treatment of cystic fibrosis (CF), a dinucleotide with full agonist activity at P2Y₂ and P2Y₄ receptors (EC₅₀ = 0.22 and 0.8 μM, respectively, for intracellular Ca²⁺ mobilization in astrocytoma cells expressing human receptors) and selectivity over P2Y₁ and P2Y₆ receptors. Compound stimulated chloride secretion in canine tracheal epithelium (EC₅₀ = 1.9 μM), mucin secretion from human airways cell cultures (EC₅₀ = 2.67 μM) and ciliary beat frequency in human airways explants (EC₅₀ = 8.3 μM). Compared to the natural P2Y agonist UTP, it was 50-fold more stable in the mucosal surface of the human nasal epithelium; in sputum samples obtained from CF patients, it was extremely stable, with a half-life of 25 h. Moreover, in sheep, nebulized compound provided a dose-dependent increase in tracheal mucus velocity, with a significant enhancement over 8 h after doses of 94 and 471 μmol. Currently in clinical evaluation in CF patients.

SOURCE – Inspire Pharmaceuticals.

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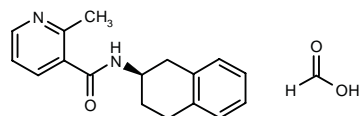
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CARDIOVASCULAR DRUGS

TREATMENT OF DISORDERS OF THE CORONARY ARTERIES AND ATHEROSCLEROSIS

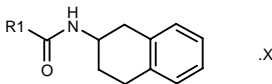
325974

2-Methyl-*N*-[1,2,3,4-tetrahydronaphthalen-2(*R*)-yl]pyridin-3-carboxamide formate



C17 H18 N2 O . C H2 O2; Mol wt: 312.3670

ACTION – Upregulator of endothelial nitric oxide synthase (eNOS) expression that was shown to stimulate eNOS expression in human umbilical vein endothelial cells (HUVEC) with an EC₅₀ of 0.18 µM. *In vivo*, oral administration of compound to apolipoprotein E (apo E)-deficient mice resulted in lowered blood pressure, inhibition of cuff-induced maladaptive neointima formation, reduction in atherosclerotic plaque formation and improvement in coronary function, reflected in increased coronary flow and reduced incidence of ventricular arrhythmias. It is reportedly useful for the treatment of angina pectoris, coronary heart disease, acute coronary syndrome, heart failure, myocardial infarction, stroke, thrombosis, peripheral artery occlusive disease, endothelial dysfunction, atherosclerosis, restenosis, hypertension, chronic glomerulonephritis, erectile dysfunction, ventricular arrhythmia, diabetes and complications related therewith. Other exemplified acylated 1,2,3,4-tetrahydronaphthylamines are:



Compound	R1	X	Isomer	Formula
325977	5-Me-2-pyrazinyl	formate	S	C ₁₆ H ₁₇ N ₃ O.CH ₂ O ₂
325979	4-CF3-2-Me-5-thiazolyl		R	C ₁₆ H ₁₅ F ₃ N ₂ OS
325980	4-CF3-2-Me-5-thiazolyl		S	C ₁₆ H ₁₅ F ₃ N ₂ OS
325981	6-CN-3-Pyr	formate	S	C ₁₇ H ₁₅ N ₃ O.CH ₂ O ₂
325983	5-(2-thienyl)-3-Pyr	formate	S	C ₂₀ H ₁₈ N ₂ OS.CH ₂ O ₂
325985	4-Pyr	formate	S	C ₁₆ H ₁₆ N ₂ O.CH ₂ O ₂

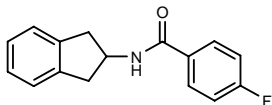
SOURCE – Aventis Pharma.

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325987

N-(2,3-Dihydro-1*H*-inden-2-yl)-4-fluorobenzamide



C16 H14 F N O; Mol wt: 255.2906

ACTION – Upregulator of endothelial nitric oxide synthase (eNOS) expression that was shown to stimulate eNOS expression in human umbilical vein endothelial cells (HUVEC) with an EC₅₀ of 0.8 µM. *In vivo*, oral administration of compound to apolipoprotein E (apo E)-deficient mice resulted in lowered blood pressure, inhibition of cuff-induced maladaptive neointima formation, reduction in atherosclerotic plaque formation and improvement in coronary function, reflected in increased coronary flow and reduced incidence of ventricular arrhythmias. It is reportedly useful for the treatment of angina pectoris, coronary heart disease, acute coronary syndrome, heart failure, myocardial infarction, stroke, thrombosis, peripheral artery occlusive disease, endothelial dysfunction, atherosclerosis, restenosis, hypertension, chronic glomerulonephritis, erectile dysfunction, ventricular arrhythmia, diabetes and complications related therewith.

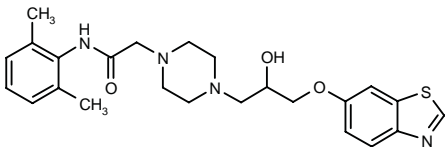
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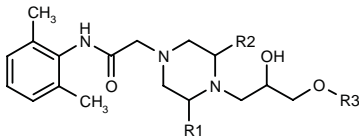
326200

2-[4-[3-(Benzothiazol-6-yloxy)-2-hydroxypropyl]piperazin-1-yl]-*N*-(2,6-dimethylphenyl)acetamide



C24 H30 N4 O3 S; Mol wt: 454.5920

ACTION – Fatty acid oxidation inhibitor proven to inhibit the oxidation of palmitoyl-CoA in rat heart mitochondria by 70% at a concentration of 100 µM. It was more stable than the reference compound ranolazine in human liver microsomes. Potentially useful for protecting skeletal muscle from damage induced by trauma, muscle or systemic diseases and other conditions, and considered to have potential in the treatment of cardiovascular diseases including atrial and ventricular arrhythmias, angina, congestive heart disease and myocardial infarction, as well as for preserving tissues and organs for transplantation. Other exemplified piperazine derivatives are:



Compound	R1	R2	R3	Formula
326202	H	H	2-benzothiazolyl	C ₂₄ H ₃₀ N ₄ O ₃ S
326203	H	H	2-Me-5-benzothiazolyl	C ₂₅ H ₃₂ N ₄ O ₃ S
326204	H	H	2-(NH2CO)-4-indolyl	C ₂₆ H ₃₃ N ₅ O ₄
326205	Me	Me	2-Me-5-benzothiazolyl	C ₂₇ H ₃₆ N ₄ O ₃ S
326206	H	H	2-quinoxaliny	C ₂₅ H ₃₁ N ₅ O ₃
326207	H	H	4-quinolyl	C ₂₆ H ₃₂ N ₄ O ₃
326208	H	H	5-isoquinolyl	C ₂₆ H ₃₂ N ₄ O ₃
326210	H	H	6-quinolyl	C ₂₆ H ₃₂ N ₄ O ₃
326211	H	H	2-Me-7-quinoliny	C ₂₇ H ₃₄ N ₄ O ₃

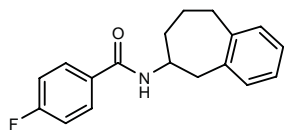
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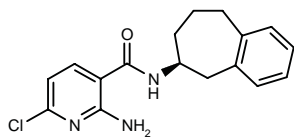
326235

(-)-4-Fluoro-*N*-(6,7,8,9-tetrahydro-5*H*-benzocyclohepten-6-yl)benzamide



C18 H18 F N O; Mol wt: 283.3442

ACTION – Upregulator of endothelial nitric oxide synthase (eNOS) expression in endothelial cells, as demonstrated in a luciferase reporter gene assay in human umbilical vein endothelial cells (HUVEC; EC₅₀ = 0.001 μM). Potentially useful for the treatment of cardiovascular disorders including angina pectoris, coronary heart disease, acute coronary syndrome, heart failure, myocardial infarction, stroke, thrombosis, peripheral occlusive artery disease, endothelial dysfunction, atherosclerosis, restenosis, post-PTCA endothelial damage, hypertension, pulmonary hypertension, chronic glomerulonephritis, erectile dysfunction, ventricular arrhythmia, diabetes, angiogenesis, asthma, osteoporosis, etc. Another exemplified compound is:



326236: C17 H18 Cl N3 O

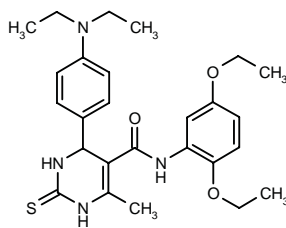
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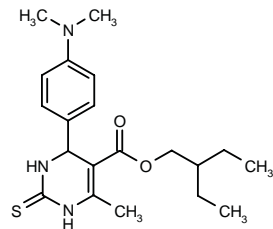
326351

N-(2,5-Diethoxyphenyl)-4-[4-(diethylamino)phenyl]-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide



C26 H34 N4 O3 S; Mol wt: 482.6456

ACTION – Neutral sphingomyelinase inhibitor (IC₅₀ = 0.86 μM) with potential in the treatment of arteriosclerosis, cerebral and cardiac ischemia, lung injury, renal injury, graft-versus-host disease and HIV infection. Another exemplified tetrahydropyrimidine derivative is:



326354: C20 H29 N3 O2 S

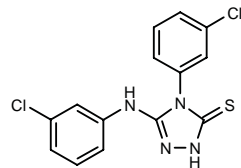
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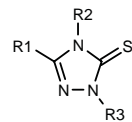
326393

4-(3-Chlorophenyl)-3-(3-chlorophenylamino)-4,5-dihydro-1*H*-1,2,4-triazole-5-thione



C14 H10 Cl2 N4 S; Mol wt: 337.2330

ACTION – Neutral sphingomyelinase inhibitor (IC₅₀ = 2.8 μM) with potential in the treatment of arteriosclerosis, cerebral and cardiac ischemia, lung injury, renal injury, graft-versus-host disease and HIV infection. Other exemplified triazole derivatives are:



Compound	R1	R2	R3	Formula
326395	2-thienyl	1,3-benzodioxol-5-yl-CH2	H	C ₁₄ H ₁₁ N ₃ O ₂ S ₂
326396	4-Cl-PhNH	4-Cl-Ph	H	C ₁₄ H ₁₀ Cl ₂ N ₄ S
326397	CH2Ph	Ph	H	C ₁₅ H ₁₃ N ₃ S
326398	4-Cl-2-OH-Ph	Ph	H	C ₁₄ H ₁₀ ClN ₃ OS
326399	4-(CF3O)-PhOCH2	i-Pr	H	C ₁₃ H ₁₄ F ₃ N ₃ O ₂ S
326400	4-Br-PhOCH2	Ph	H	C ₁₅ H ₁₂ BrN ₃ OS
326401	3-indolyl-CH2	Ph	H	C ₁₇ H ₁₄ N ₄ S
326402	3,5-(CF3)2-Ph	H	H	C ₁₀ H ₅ F ₆ N ₃ S
326403	4-t-Bu-Ph	H	H	C ₁₂ H ₁₅ N ₃ S
326405	Ph	H	H	C ₈ H ₇ N ₃ S
326406	2-thienyl	Ph	H	C ₁₂ H ₉ N ₃ S ₂
326407	NHPh	Ph	H	C ₁₄ H ₁₂ N ₄ S
326408	2-Br-PhNH	2-Br-Ph	H	C ₁₄ H ₁₀ Br ₂ N ₄ S
326409	NHPh	Ph	CH2OH	C ₁₅ H ₁₄ N ₄ OS

SOURCE – Ono.

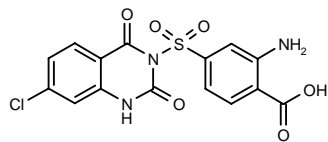
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SUN-C8257*

286919

2-Amino-4-(7-chloro-2,4-dioxo-1,2,3,4-tetrahydro-quinazolin-3-ylsulfonyl)benzoic acid



C15 H10 Cl N3 O6 S; Mol wt: 395.7780

ACTION – Potent chymase inhibitor ($IC_{50} = 0.31 \mu M$) with selectivity over chymotrypsin and cathepsin G ($IC_{50} = 23$ and $5.5 \mu M$, respectively). In a dog model of heart failure induced by chronic tachycardia, compound (10 mg/kg/day) significantly reduced the number of chymase-degranulated cells, improved the prolonged time constant of relaxation and reduced mRNA levels of TGF- β and collagen type I and III in cardiac tissue and the total number of collagen deposits in the left ventricle. In hamsters fed a high-cholesterol diet, compound (100 mg/day p.o. for 2 weeks) suppressed aortic cholesterol deposition without inducing changes in blood pressure and plasma LDL cholesterol. Using a model of scleroderma in tight skin (Tsk) mice, a dose of 50 mg/kg/day i.p. for 2 weeks significantly reduced chymase activity, mRNA expression of the skin chymase MMCP-4 and fibrous proliferation in the skin. Other experiments showed that it significantly inhibited blood eosinophilia in *Nippostrongylus brasiliensis*-infected mice and improved dermatitis symptoms in NC/Nga mice. Potentially useful for preventing cardiac remodeling and atherosclerosis.

SOURCE – Suntory.

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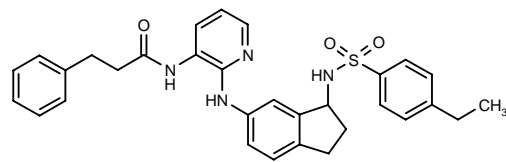
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*Identified compound **286919** (see **286917**) Drug Data Rep 2000, 022(06): 0505.

ANTIARRHYTHMIC DRUGS

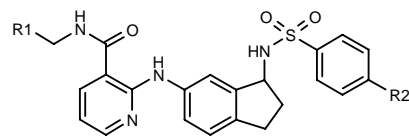
325459

N-[2-[3-(4-Ethylphenylsulfonamido)-2,3-dihydro-1H-inden-5-ylamino]pyridin-3-yl]-3-phenylpropionamide



C31 H32 N4 O3 S; Mol wt: 540.6848

ACTION – An inhibitor of voltage-gated potassium channels such as Kv1.5 and Kv1.3 that was found to inhibit Kv1.5 potassium channels expressed in CHO cells by 46% at a concentration of 0.1 μM . Potentially useful for the treatment of cardiac arrhythmia and cell proliferative disorders. Other exemplified compounds are:



Compound	R1	R2	Formula
325460	vinyl	Et	C ₂₆ H ₂₈ N ₄ O ₃ S
325470	ethynyl	Et	C ₂₆ H ₂₆ N ₄ O ₃ S
325471	Et	Et	C ₂₆ H ₃₀ N ₄ O ₃ S
325473	2-furyl	Et	C ₂₈ H ₂₈ N ₄ O ₄ S
325474	CH2Ph	F	C ₂₉ H ₂₇ FN ₄ O ₃ S
325475	2-thienyl	F	C ₂₆ H ₂₃ FN ₄ O ₃ S ₂

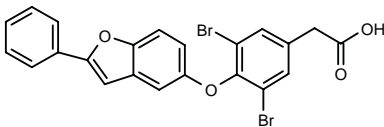
SOURCE – ICAgen.

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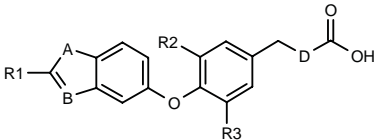
325612

2-[3,5-Dibromo-4-(2-phenyl-1-benzofuran-5-yloxy)phen-yl]acetic acid



C22 H14 Br2 O4; Mol wt: 502.1566

ACTION – Thyroid receptor antagonist, potentially useful for the treatment of cardiac arrhythmia, thyrotoxicosis, subclinical hyperthyroidism, skin disorders such as acne, psoriasis, eczema, atopic dermatitis, hirsutism, etc., and liver diseases including chronic alcoholism, acute and chronic hepatitis, hepatitis C-induced liver cirrhosis and liver fibrosis. Other specifically claimed compounds are:



Compound	R1	R2	R3	A	B	D	Formula
325614	H	Br	Br	NH	N	bond	C ₁₅ H ₁₀ Br ₂ N ₂ O ₃
325615	H	Br	Br	N(Me)	N	bond	C ₁₆ H ₁₂ Br ₂ N ₂ O ₃
325616	Me	Br	Br	NH	N	bond	C ₁₆ H ₁₂ Br ₂ N ₂ O ₃
325617	i-Pr	Cl	Cl	NH	N	bond	C ₁₈ H ₁₆ Cl ₂ N ₂ O ₃
325620	3-Me-Ph	Br	Br	O	CH	-CH2-	C ₂₄ H ₁₈ Br ₂ O ₄

SOURCE – Karo Bio.

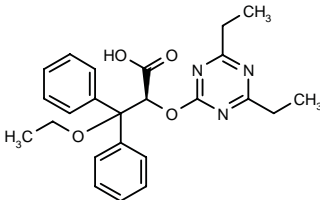
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HEART FAILURE THERAPY

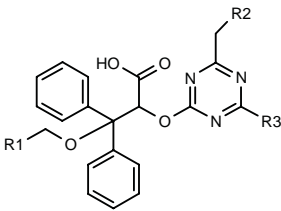
326035

2(S)-(4,6-Diethyl-1,3,5-triazin-2-yloxy)-3-ethoxy-3,3-diphenylpropionic acid



C24 H27 N3 O4; Mol wt: 421.4943

ACTION – Selective endothelin ET_A receptor antagonist with high affinity for ET_A receptors (K_i = 1.95 nM) and > 760-fold selectivity over ET_B receptors. Potentially useful for the treatment of chronic heart failure, restenosis, hypertension, pulmonary hypertension, acute and chronic renal failure, erectile dysfunction, liver cirrhosis, cerebral ischemia, benign prostatic hyperplasia, prostate cancer and acute pancreatitis. Other exemplified compounds are:



Compound	R1	R2	R3	Formula
326036	Me	H	Et	C ₂₃ H ₂₅ N ₃ O ₄
326037	Me	Me	OMe	C ₂₃ H ₂₅ N ₃ O ₅
326038	H	Me	Et	C ₂₃ H ₂₅ N ₃ O ₄
326039	Et	H	Me	C ₂₃ H ₂₅ N ₃ O ₄
326040	H	Me	OMe	C ₂₂ H ₂₃ N ₃ O ₅
326041	Me	Me	Et	C ₂₄ H ₂₇ N ₃ O ₄
326042	Me	H	Me	C ₂₂ H ₂₃ N ₃ O ₄

SOURCE – Abbott.

REFERENCES

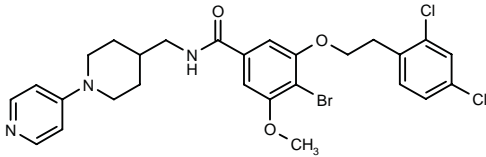
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AGENTS AFFECTING BLOOD COAGULATION

ANTICOAGULANTS

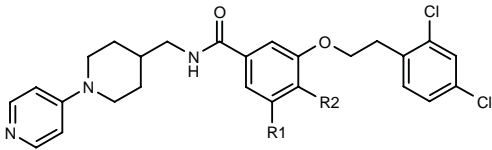
323267

4-Bromo-3-[2-(2,4-dichlorophenyl)ethoxy]-5-methoxy-N-[1-(4-pyridyl)piperidin-4-ylmethyl]benzamide



C27 H28 Br Cl2 N3 O3; Mol wt: 593.3462

ACTION – Factor Xa inhibitor (K_i = 0.020 μM) that is reportedly useful for the treatment of coagulation disorders including fibrinolysis, cardiovascular disorders, thromboembolic diseases, restenosis, inflammation, abnormal thrombus formation, myocardial infarction, angina pectoris, thromboembolism, transient ischemic attacks, stroke, viral infections, cancer, adult respiratory distress syndrome, multiorgan failure, disseminated intravascular coagulation, etc. Other exemplified compounds are:



Compound	R1	R2	Formula
323268	H	Me	C ₂₇ H ₂₉ Cl ₂ N ₃ O ₂
323269	H	NH2	C ₂₆ H ₂₈ Cl ₂ N ₄ O ₂
323270	OH	Br	C ₂₆ H ₂₆ BrCl ₂ N ₃ O ₃
323271	H	SMe	C ₂₇ H ₂₉ Cl ₂ N ₃ O ₂ S

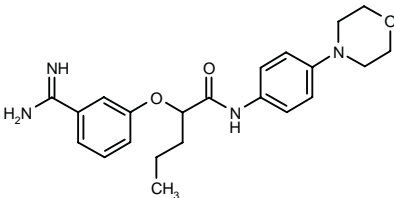
SOURCE – Aventis Pharma.

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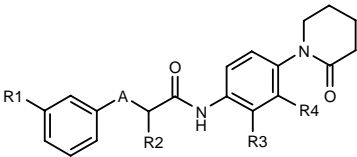
324731

2-(3-Amidinophenoxy)-N-[4-(4-morpholinyl)phenyl]-pentanamide

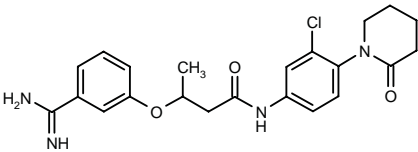


C22 H28 N4 O3; Mol wt: 396.4882

ACTION – Anticoagulant, an inhibitor of factor Xa and/or factor VIIa. Potentially useful for the treatment of thrombosis, myocardial infarction, arteriosclerosis, inflammation, stroke, angina pectoris, postangioplasty restenosis, intermittent claudication and cancer. Other specifically claimed compounds include the following:



Compound	R1	R2	R3	R4	A	Formula
324732	C(=NH)NH2	Ph	H	H	NH	C ₂₆ H ₂₇ N ₅ O ₂
324733	C(=NH)NH2	Pr	Me	H	O	C ₂₄ H ₃₀ N ₄ O ₃
324734	C(=NH)NH2	(S)-Ph	H	H	NH	C ₂₆ H ₂₇ N ₅ O ₂
324735	CONH2	Pr	H	H	NH	C ₂₃ H ₂₈ N ₄ O ₃
324736	CH2NH2	H	H	H	NH	C ₂₆ H ₂₈ N ₄ O ₂
324737	CH2NH2	CH(Me)CF3	H	H	NH	C ₂₃ H ₂₇ F ₃ N ₄ O ₂
324741	C(=NH)NH2	Pr	H	OCH2CO2Et	O	C ₂₇ H ₃₄ N ₄ O ₆



324738: C22 H25 Cl N4 O3

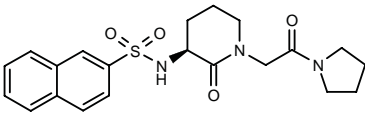
SOURCE – Merck KGaA.

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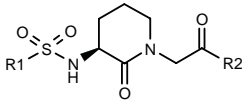
325461

N-[2-Oxo-1-[2-oxo-2-(1-pyrrolidinyl)ethyl]piperidin-3(S)-yl]naphthalene-2-sulfonamide

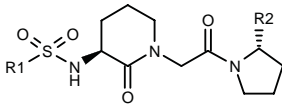


C21 H25 N3 O4 S; Mol wt: 415.5115

ACTION – Anticoagulant with factor Xa-inhibitory activity, potentially useful for the treatment of thrombosis, coronary artery disease and cerebrovascular diseases. Other exemplified sulfonamide lactams include the following:



Compound	R1	R2	Formula
325462	6-Cl-2-benzothienyl	1-(CH2CO2Et)-4-Piz	C ₂₃ H ₂₉ ClN ₄ O ₆ S ₂
325463	6-Cl-2-Naph	2-(3-NO2-Ph)-3-thiazolidinyl	C ₂₆ H ₂₅ ClN ₄ O ₆ S ₂
325464	5-Cl-2-benzothienyl	5-(MeSO2)-2,5-diaza-bicyclo[2.2.1]hept-2-yl	C ₂₁ H ₂₅ ClN ₄ O ₆ S ₃
325468	5-Cl-thieno[3,2-b]-pyridin-2-yl	7-Ac-3,7-diaza-bicyclo[3.3.1]non-3-yl	C ₂₃ H ₂₈ ClN ₅ O ₅ S ₂



Compound	R1	R2	Formula
325465	5-(5-Cl-2-thienyl)-2-thienyl	perhydroazepin-1-yl-CH2	C ₂₆ H ₃₅ ClN ₄ O ₄ S ₃
325466	5-Cl-2-thienyl-CH=CH	cyclopropyl-CH2NHCO	C ₂₂ H ₂₉ ClN ₄ O ₅ S ₂
325467	5-Cl-2-thienyl-CH=CH	3-[3,5-(Me)2-4-isoxazolyl-SO2-N(Me)]-3-pyrrolidinyl-CH2	C ₂₈ H ₃₉ ClN ₆ O ₇ S ₃
325469	5-Cl-2-benzothienyl	4-(cyclopropyl-CO)-1-Piz-CH2	C ₂₈ H ₃₆ ClN ₅ O ₅ S ₂
325472	5-(5-Cl-2-thienyl)-2-thienyl	4-Me-PhSO2CH2-CONHCH2	C ₂₉ H ₃₃ ClN ₄ O ₇ S ₄

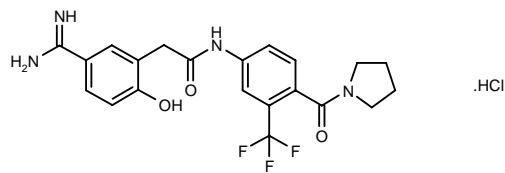
SOURCE – Bristol-Myers Squibb.

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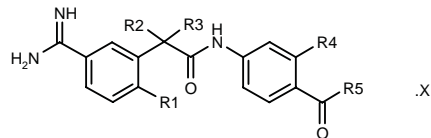
325633

2-(5-Amidino-2-hydroxyphenyl)-N-[4-(pyrrolidin-1-ylcarbonyl)-3-(trifluoromethyl)phenyl]acetamide hydrochloride



C21 H21 F3 N4 O3 . HCl; Mol wt: 470.8768

ACTION – Agent with factor Xa-inhibitory activity (IC₅₀ = 0.011 μM), potentially useful for the treatment of thrombotic disorders. Other exemplified compounds are:



Compound	R1	R2	R3	R4	R5	X	Formula
325634	H	Me	Me	Me	3-Me-1-pyrrolidinyl	HCl	C ₂₄ H ₃₀ N ₄ O ₂ .HCl
325635	OH	H	H	Me	3-Pip		C ₂₂ H ₂₆ N ₄ O ₃
325636	OH	H	H	Cl	1-pyrrolidinyl	HCl	C ₂₀ H ₂₁ ClN ₄ O ₃ .HCl

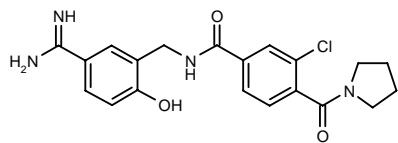
SOURCE – Boehringer Ingelheim.

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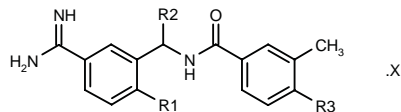
325638

N-(5-Amidino-2-hydroxybenzyl)-3-chloro-4-(pyrrolidin-1-ylcarbonyl)benzamide

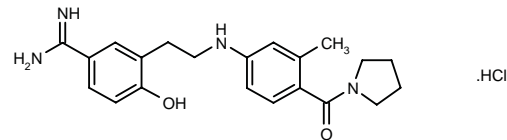


C20 H21 Cl N4 O3; Mol wt: 400.8639

ACTION – Agent with factor Xa-inhibitory activity (IC₅₀ = 0.01 μM), potentially useful for the treatment of thrombotic disorders. Other exemplified compounds are:



Compound	R1	R2	R3	X	Formula
325640	OH	H	1-pyrrolidinyl-CO	HCl	C ₂₁ H ₂₄ N ₄ O ₃ .HCl
325641	OH	H	N(cyclopentyl)-COCH ₂ CH ₂ CO ₂ Et	HCl	C ₂₇ H ₃₄ N ₄ O ₅ .HCl
325642	H	CH ₂ CO ₂ H	1-pyrrolidinyl-CO		C ₂₃ H ₂₆ N ₄ O ₄



325639: C21 H26 N4 O2 . HCl

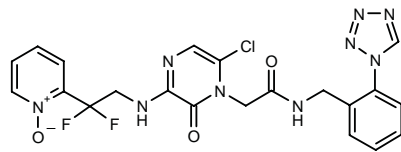
SOURCE – Boehringer Ingelheim.

REFERENCES

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325958

2-[6-Chloro-3-[2,2-difluoro-2-(1-oxidopyridin-2-yl)ethyl-amino]-2-oxo-1,2-dihydropyrazin-1-yl]-N-[2-(1 H-tetrazol-1-yl)benzyl]acetamide



C21 H18 Cl F2 N9 O3; Mol wt: 517.8822

ACTION – Anticoagulant with thrombin-inhibitory activity and potential utility in the treatment of thromboembolic disorders including venous thromboembolism, pulmonary embolism, deep venous thrombosis and thromboembolic stroke.

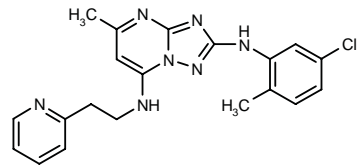
SOURCE – Merck & Co.

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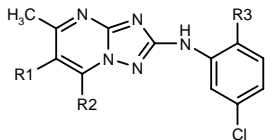
325965

N²-(5-Chloro-2-methylphenyl)-5-methyl-N⁷-[2-(2-pyridyl)-ethyl][1,2,4]triazolo[1,5-a]pyrimidine-2,7-diamine



C20 H20 Cl N7; Mol wt: 393.8800

ACTION – Thrombin inhibitor considered to have potential in the treatment of thromboembolic disorders including venous thromboembolism, pulmonary embolism, deep venous thrombosis and thromboembolic stroke. Other exemplified compounds are:



Compound	R1	R2	R3	Formula
325967	H	1-oxido-2-Pyr-CF2CH2NH	Me	C ₂₀ H ₁₈ ClF ₂ N ₇ O
325968	H	2-Pyr-CH2CH2NH	3-Pyr-O	C ₂₄ H ₂₁ ClN ₆ O
325969	CH2Ph	NH2	3-Pyr-O	C ₂₄ H ₂₀ ClN ₇ O

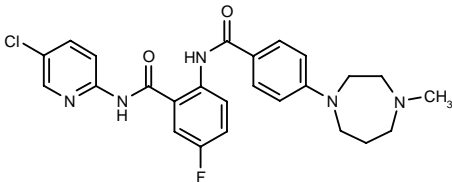
SOURCE – Merck & Co.

REFERENCES

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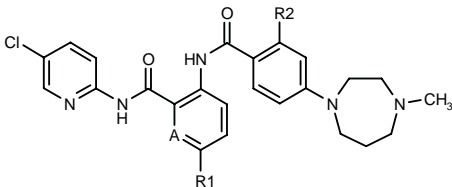
325997

N-(5-Chloropyridin-2-yl)-5-fluoro-2-[4-(4-methylperhydro-1,4-diazepin-1-yl)benzamido]benzamide



C25 H25 Cl F N5 O2; Mol wt: 481.9565

ACTION – Factor Xa inhibitor with potential in the treatment of thromboembolic disorders including thrombosis, pulmonary embolism, myocardial ischemia, myocardial infarction, unstable angina, stroke, peripheral arterial thrombosis, atherosclerotic disorders, etc. Other specifically claimed substituted carboxamides are:



Compound	R1	R2	A	Formula
325998	H	H	N	C ₂₄ H ₂₅ ClN ₆ O ₂
325999	F	CF3	CH	C ₂₈ H ₂₄ ClF ₄ N ₅ O ₂
326000	Cl	CF3	CH	C ₂₆ H ₂₄ Cl ₂ F ₃ N ₅ O ₂
326001	F	OEt	CH	C ₂₇ H ₂₉ ClFN ₅ O ₃
326002	F	i-PrO	CH	C ₂₈ H ₃₁ ClFN ₅ O ₃
326003	F	OCH2CH2OMe	CH	C ₂₈ H ₃₁ ClFN ₅ O ₄

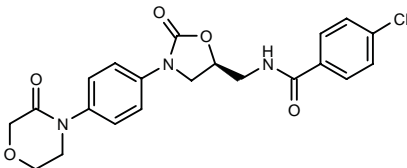
SOURCE – Lilly.

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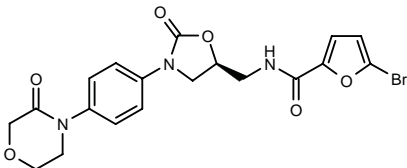
326197

4-Chloro-N-[2-oxo-3-[4-(3-oxomorpholin-4-yl)phenyl]-oxazolidin-5(S)-ylmethyl]benzamide



C21 H20 Cl N3 O5; Mol wt: 429.8580

ACTION – Factor Xa inhibitor (IC₅₀ = 20 nM), potentially useful for the treatment of thromboembolic disorders, particularly myocardial infarction, angina pectoris, post-angioplasty restenosis, stroke, peripheral vascular diseases, pulmonary embolism, deep venous thrombosis, atherosclerosis, arthritis, Alzheimer's disease and cancer. Another exemplified compound is:



326198: C19 H18 Br N3 O6

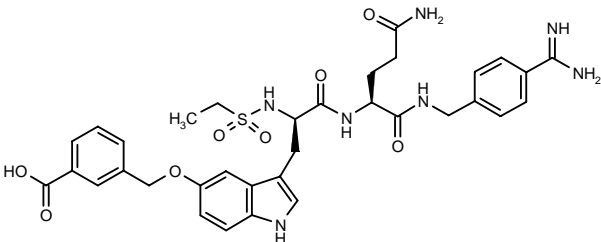
SOURCE – Bayer.

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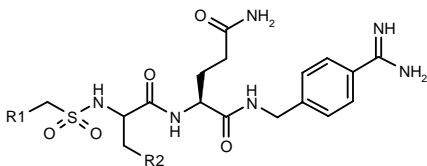
326452

N¹-(4-Amidinobenzyl)-N²-[5-(3-carboxybenzyloxy)-N-(ethylsulfonyl)-D-tryptophyl]-L-glutaminamide



C34 H39 N7 O8 S; Mol wt: 705.7891

ACTION – Peptide derivative with factor VIIa-inhibitory activity, giving an IC₅₀ of 39 nM against factor VIIa and exhibiting 450-fold selectivity over thrombin. Potentially useful for the treatment of coagulation disorders including postoperative deep venous thrombosis, post-PTCA restenosis, chronic thrombosis, thromboembolism, myocardial infarction and cerebral infarction. Other exemplified peptide derivatives are:



Compound	R1	R2	Isomer	Formula
326453	Me	3-indolyl	D	C ₂₆ H ₃₃ N ₇ O ₅ S
326454	3-CO ₂ H-Ph	3-indolyl	D	C ₃₂ H ₃₅ N ₇ O ₇ S
326455	Me	4-Ph-Ph	D	C ₃₀ H ₃₆ N ₆ O ₅ S
326456	Me	4-(PhCO)-Ph	D	C ₃₁ H ₃₆ N ₆ O ₆ S
326457	Me	5-Me-3-indolyl	DL	C ₂₇ H ₃₅ N ₇ O ₅ S
326458	Me	5-(PhCH ₂ O)-3-indolyl	D	C ₃₃ H ₃₉ N ₇ O ₆ S
326459	CO ₂ H	3-indolyl	D	C ₂₆ H ₃₁ N ₇ O ₇ S
326461	Me	5-MeO-3-indolyl	D	C ₂₇ H ₃₅ N ₇ O ₆ S
326462	Me	5-PrO-3-indolyl	D	C ₂₉ H ₃₉ N ₇ O ₆ S

SOURCE – Chugai.

REFERENCES

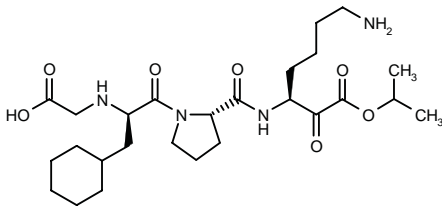
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ORG-39430

287068

N-(Carboxymethyl)-3-cyclohexyl-D-alanyl-*N*-[5-amino-1(*S*)-(2-isopropoxyoxalyl)pentyl]-L-prolinamide

7-Amino-3(*S*)-[*N*-(carboxymethyl)-3-cyclohexyl-D-alanyl-L-prolylamino]-2-oxoheptanoic acid isopropyl ester



C26 H44 N4 O7; Mol wt: 524.6546

ACTION – Thrombin inhibitor, a tripeptide transition-state analogue with *K_i* of 1.1 nM against human enzyme and 50-1,000-fold selectivity over human-derived serine proteases including factor Xa, factor VIIIa/tissue factor, plasmin, tissue-type plasminogen activator (tPA) and activated protein C. Compound exhibited good pharmacokinetic parameters in rats and dogs, with oral bioavailability of 32 and 71%, respectively and a half-life of 458 and 108 min, respectively. In the aortic flow model in rats, it showed good antithrombotic efficacy comparable to argatroban and melagatran (ED₅₀ = 5.4, 27 and 5.2 nmol/kg/min i.v., respectively).

SOURCE – Organon.

REFERENCES

1. Van Boeckel, C.A.A. et al. (Akzo Nobel N.V.) *Thrombin inhibitors.* WO 9807308.

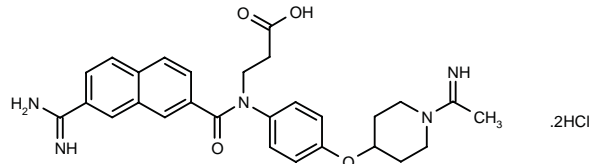
2. Adang, A.E.P. et al. *A polar pharmacophore for oral bioavailability in thrombin inhibitors.* 15th EFMC Int Symp Med Chem (Sept 6-10, Edinburgh) 1998, Abst P.157.

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YM-169964*

275488

N-(7-Amidinonaphthalen-2-ylcarbonyl)-*N*-[4-(1-iminoethylpiperidin-4-yloxy)phenyl]-β-alanine dihydrochloride



C28 H31 N5 O4 . 2HCl; Mol wt: 574.5057

ACTION – Anticoagulant, a potent factor Xa inhibitor (IC₅₀ = 3.9 nM) with high selectivity relative to trypsin and thrombin (IC₅₀ = 291 and > 100,000 nM, respectively). It gave a CT2 value (concentration required to double coagulation time) of 0.062 μM when tested in human plasma. Compound exhibited a good pharmacokinetic profile after oral administration in dogs and prolonged prothrombin time by 9.6-fold *ex vivo* after an oral dose of 3 mg/kg in monkeys.

SOURCE – Yamanouchi.

REFERENCES

1. Hirayama, F. et al. (Yamanouchi Pharmaceutical Co., Ltd.) *Novel naphthamide derivs. or salts thereof.* WO 9911617.

2. Hirayama, F. et al. *Design, synthesis and biological activity of YM-60828 derivatives: Potent and orally-bioavailable factor Xa inhibitors based on naphthoanilide and naphthalensulfonanilide templates.* Bioorg Med Chem 2002, 10(8): 2597.

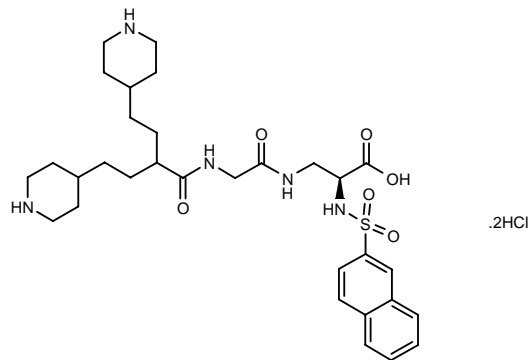
*Identified compound **275488** Drug Data Rep 1999, 021(06): 0511.

ANTIPLATELET THERAPY

CRL-42796

305660

N-[4-(4-Piperidiny)-2-[2-(4-piperidiny)ethyl]butyryl]glycyl-2(*S*)-(naphthalen-2-ylsulfonyl)-β-alanine dihydrochloride



C31 H45 N5 O6 S . 2HCl; Mol wt: 688.7133

ACTION – Platelet gpIIb/IIIa receptor antagonist proven to inhibit *ex vivo* platelet aggregation induced by arachidonic acid and ADP, with only a marginal effect on bleeding time. In dog models of carotid and coronary artery thrombosis induced by electrolytic vessel wall injury, 15 µg/kg + 0.69 µg/kg/min i.v. prevented occlusive thrombosis and significantly increased time to thrombosis compared to control group; the addition of oral aspirin failed to produce an additional antithrombotic effect. Potentially useful as an antithrombotic agent.

SOURCE – Lafon.

REFERENCES

1. Grandati, M. et al. *Antiplatelet activity of CRL42796, a novel non peptide GPIIb/IIIa inhibitor*. Thromb Haemost 2001, (Suppl.): Abst P1210.

2. Grandati, M. et al. *Antiplatelet effects of the GPIIb/IIIa antagonist CRL42796 translated into antithrombotic properties*. Pathophysiol Haemost Thromb 2002, 32(Suppl. 2): Abst P131.

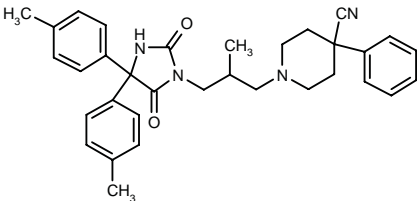
3. Hennen, J.K. et al. *Prevention of experimental carotid and coronary artery thrombosis by the glycoprotein IIb/IIIa receptor antagonist CRL42796*. Br J Pharmacol 2002, 136(6): 927.

RENAL-UROLOGIC DRUGS

BENIGN PROSTATIC HYPERPLASIA THERAPY

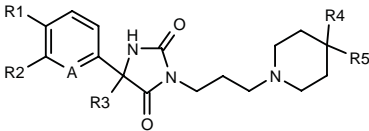
325873

(±)-1-[3-[4,4-Bis(4-methylphenyl)-2,5-dioxoimidazolidin-1-yl]-2-methylpropyl]-4-phenylpiperidine-4-carbonitrile

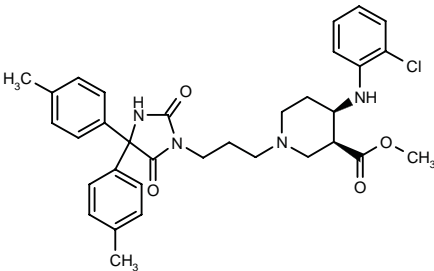


C33 H36 N4 O2; Mol wt: 520.6734

ACTION – α_{1A}-Adrenoceptor antagonist reported to display intraurethral pressure-lowering activity while being devoid of hypotensive activity. Potentially useful for the treatment of benign prostatic hyperplasia. Other specifically claimed arylhydantoin derivatives are:



Compound	R1	R2	R3	R4	R5	A	Formula
325879	H	H	4-Me-Ph	2-Me-Ph	CN	N	C ₃₁ H ₃₃ N ₅ O ₂
325880	H	H	Me	Ph	CN	CH	C ₂₅ H ₂₈ N ₄ O ₂
325881	Me	H	i-Pr	2-Me-Ph	CN	CH	C ₂₉ H ₃₆ N ₄ O ₂
325883	Me	H	C5H11	2-Me-Ph	CN	CH	C ₃₁ H ₄₀ N ₄ O ₂
325884	F	F	C5H11	2-Me-Ph	CN	CH	C ₃₀ H ₃₆ F ₂ N ₄ O ₂
325887	Cl	H	C5H11	2-Me-Ph	CN	CH	C ₃₀ H ₃₇ ClN ₄ O ₂
325898	Me	H	4-Me-Ph	5-Cl-2-oxo-2,3-dihydro-1-benzimidazolyl	H	CH	C ₃₂ H ₃₄ ClN ₅ O ₃



325893: C33 H37 Cl N4 O4

SOURCE – Merck & Co.

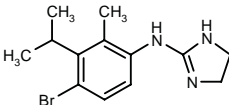
REFERENCES

1. Hoffman, J.M. et al. (Merck & Co., Inc.) *Arylhydantoin derivs. and use thereof*. US 6436962.

TREATMENT OF URINARY INCONTINENCE

326004

N-(4-Bromo-3-isopropyl-2-methylphenyl)-4,5-dihydro-1*H*-imidazol-2-amine



C13 H18 Br N3; Mol wt: 296.2102

ACTION – Agent for the treatment of urinary incontinence that demonstrated activity in human urethra (*in vitro*) and in dogs. Other exemplified imidazolidine derivatives are:

ACTION – Platelet gpIIb/IIIa receptor antagonist proven to inhibit *ex vivo* platelet aggregation induced by arachidonic acid and ADP, with only a marginal effect on bleeding time. In dog models of carotid and coronary artery thrombosis induced by electrolytic vessel wall injury, 15 µg/kg + 0.69 µg/kg/min i.v. prevented occlusive thrombosis and significantly increased time to thrombosis compared to control group; the addition of oral aspirin failed to produce an additional antithrombotic effect. Potentially useful as an antithrombotic agent.

SOURCE – Lafon.

REFERENCES

1. Grandati, M. et al. *Antiplatelet activity of CRL42796, a novel non peptide GPIIb/IIIa inhibitor*. Thromb Haemost 2001, (Suppl.): Abst P1210.

2. Grandati, M. et al. *Antiplatelet effects of the GPIIb/IIIa antagonist CRL42796 translated into antithrombotic properties*. Pathophysiol Haemost Thromb 2002, 32(Suppl. 2): Abst P131.

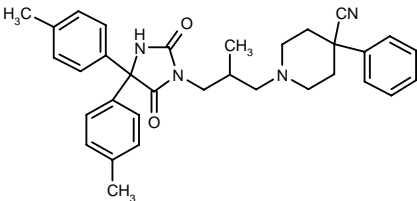
3. Hennen, J.K. et al. *Prevention of experimental carotid and coronary artery thrombosis by the glycoprotein IIb/IIIa receptor antagonist CRL42796*. Br J Pharmacol 2002, 136(6): 927.

RENAL-UROLOGIC DRUGS

BENIGN PROSTATIC HYPERPLASIA THERAPY

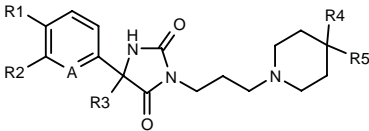
325873

(±)-1-[3-[4,4-Bis(4-methylphenyl)-2,5-dioximidazolidin-1-yl]-2-methylpropyl]-4-phenylpiperidine-4-carbonitrile

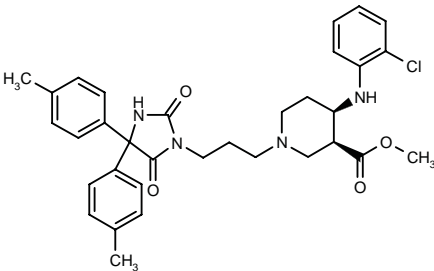


C33 H36 N4 O2; Mol wt: 520.6734

ACTION – α_{1A}-Adrenoceptor antagonist reported to display intraurethral pressure-lowering activity while being devoid of hypotensive activity. Potentially useful for the treatment of benign prostatic hyperplasia. Other specifically claimed arylhydantoin derivatives are:



Compound	R1	R2	R3	R4	R5	A	Formula
325879	H	H	4-Me-Ph	2-Me-Ph	CN	N	C ₃₁ H ₃₃ N ₅ O ₂
325880	H	H	Me	Ph	CN	CH	C ₂₅ H ₂₈ N ₄ O ₂
325881	Me	H	i-Pr	2-Me-Ph	CN	CH	C ₂₉ H ₃₆ N ₄ O ₂
325883	Me	H	C5H11	2-Me-Ph	CN	CH	C ₃₁ H ₄₀ N ₄ O ₂
325884	F	F	C5H11	2-Me-Ph	CN	CH	C ₃₀ H ₃₆ F ₂ N ₄ O ₂
325887	Cl	H	C5H11	2-Me-Ph	CN	CH	C ₃₀ H ₃₇ ClN ₄ O ₂
325898	Me	H	4-Me-Ph	5-Cl-2-oxo-2,3-dihydro-1-benzimidazolyl	H	CH	C ₃₂ H ₃₄ ClN ₅ O ₃



325893: C33 H37 Cl N4 O4

SOURCE – Merck & Co.

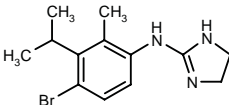
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1. Hoffman, J.M. et al. (Merck & Co., Inc.) *Arylhdyantoin derivs. and use thereof*. US 6436962.

TREATMENT OF URINARY INCONTINENCE

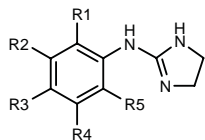
326004

N-(4-Bromo-3-isopropyl-2-methylphenyl)-4,5-dihydro-1*H*-imidazol-2-amine



C13 H18 Br N3; Mol wt: 296.2102

ACTION – Agent for the treatment of urinary incontinence that demonstrated activity in human urethra (*in vitro*) and in dogs. Other exemplified imidazolidine derivatives are:



Compound	R1	R2	R3	R4	R5	Formula
326005	Me	i-Pr	H	H	H	C ₁₃ H ₁₉ N ₃
326006	OMe	H	H	t-Bu	H	C ₁₄ H ₂₁ N ₃ O
326007	Me	i-Pr	H	H	Cl	C ₁₃ H ₁₈ ClN ₃
326008	Me	i-Pr	Cl	H	H	C ₁₃ H ₁₈ ClN ₃
326009	Me	i-Pr	H	H	Br	C ₁₃ H ₁₈ BrN ₃
326010	H	t-Bu	H	H	Br	C ₁₃ H ₁₈ BrN ₃

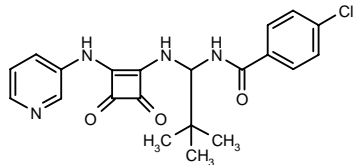
SOURCE – Boehringer Ingelheim.

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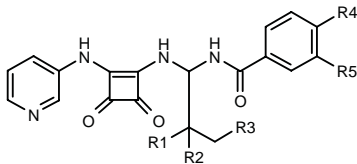
326043

4-Chloro-*N*-[1-[3,4-dioxo-2-(pyridin-3-ylamino)-1-cyclobuten-1-ylamino]-2,2-dimethylpropyl]benzamide



C21 H21 Cl N4 O3; Mol wt: 412.8749

ACTION – Potassium channel opener that gave an EC₅₀ value of 0.16 μM in membrane hyperpolarization assays using pig urinary bladder cells. In functional assays using pig isolated bladder strips, compound gave an EC₅₀ value of 6.9 μM. Potentially useful for the treatment of bladder overactivity, benign prostatic hyperplasia, dysmenorrhea, preterm labor, urinary incontinence, male erectile dysfunction, premature ejaculation and female sexual dysfunction. Other exemplified compounds are:



Compound	R1	R2	R3	R4	R5	Formula
326044	Me	Me	H	Me	H	C ₂₂ H ₂₄ N ₄ O ₃
326045	allyl	Me	H	Cl	H	C ₂₃ H ₂₃ ClN ₄ O ₃
326046	CH2Ph	Me	H	Cl	H	C ₂₇ H ₂₅ ClN ₄ O ₃
326047	allyl-OCH2	allyl-OCH2	Me	Cl	H	C ₂₈ H ₃₁ ClN ₄ O ₅
326049	CH2Ph	Me	H	H	Me	C ₂₈ H ₂₈ N ₄ O ₃

SOURCE – Abbott.

REFERENCES

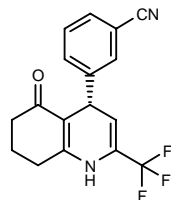
1. Kort, M.E. et al. (Abbott Laboratories) *Aminal diones as potassium channel openers*. WO 0262761.

ZD-0947*

230610

3-[5-Oxo-2-(trifluoromethyl)-1,4,5,6,7,8-hexahydroquinolin-4(S)-yl]benzonitrile

AZD-0947



C17 H13 F3 N2 O; Mol wt: 318.2967

ACTION – ATP-sensitive potassium channel (K_{ATP}) opener with *in vivo* efficacy in a rat model of bladder overactivity induced by overfilling under isovolumetric conditions. In this experiment, compound at a dose of 2.9 mg/kg i.v. was 3-5-fold more uroselective than (–)-cromakalim. Potentially useful for the treatment of urinary incontinence.

SOURCE – AstraZeneca.

REFERENCES

1. Ohnmacht, C.J. et al. (AstraZeneca plc) *Quinolone and acridinone derivs. for the treatment of urinary incontinence*. EP 0665834, JP 1996502282, US 5622964, WO 9408966.

2. Warawa, J.E. et al. (AstraZeneca plc) *Quinolone deriv. for treatment of urinary incontinence*. EP 0755382, JP 1997512254, WO 9528388.

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6. *87 development projects under way at Zeneca*. DailyDrugNews.com (Daily Essentials) 1997, Dec 16.

7. *AstraZeneca takes an ambitious approach to drug R&D*. DailyDrugNews.com (Daily Essentials) 1999, Dec 13.

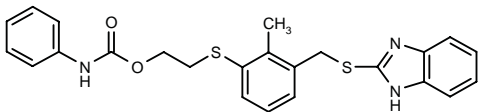
*Identified compound **230610** Drug Data Rep 1996, 018(03): 0247.

GASTROINTESTINAL DRUGS

ANTIULCER DRUGS

324623

N-Phenylcarbamic acid 2-[3-(1*H*-benzimidazol-2-ylsulfanylmethyl)-2-methylphenylsulfanyl]ethyl ester



C24 H23 N3 O2 S2; Mol wt: 449.5967

ACTION – Antibacterial agent active against a broad panel of *Helicobacter pylori* strains, including metronidazole- and clarithromycin-resistant strains (MIC = 0.5 μM) but practically inactive against clinically important aerobic and anaerobic microorganisms (MIC > 64 μg/ml). It also exhibited bactericidal activity and killing rates similar to clarithromycin and amoxicillin. Compound showed a favorable pharmacokinetic profile, with a C_{max} of 0.9 ng/ml, approximately 2-fold higher than the MIC against *H. pylori* *in vitro*.

SOURCE – AstraZeneca.

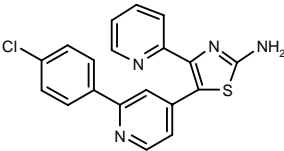
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1. Abedi, J. et al. (Pharmacia AB) *Compounds*. WO 0134573.
2. Carcanague, D. et al. *Novel structures derived from 2-[[2-(pyridyl)methyl]thio]-1*H*-benzimidazole as anti-*Helicobacter pylori* agents, part 2*. J Med Chem 2002, 45(19): 4300.

TREATMENT OF LIVER AND BILIARY TRACT DISORDERS

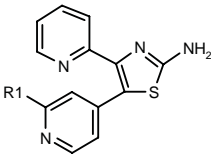
325739

5-[2-(4-Chlorophenyl)pyridin-4-yl]-4-(2-pyridyl)thiazol-2-amine



C19 H13 Cl N4 S; Mol wt: 364.8587

ACTION – Agent with the ability to interfere with the TGF-β signaling pathway through inhibition of ALK5 kinase, potentially useful for the treatment of fibrosis, particularly liver and kidney fibrosis, and also cancer, abnormal bone function, inflammatory disorders and scarring. Other specifically claimed thiazolamines are:



Compound	R1	Formula
325742	4-MeO-Ph	C ₂₀ H ₁₆ N ₄ OS
325743	4-F-Ph	C ₁₉ H ₁₃ FN ₄ S
325744	4-Et-Ph	C ₂₁ H ₁₈ N ₄ S
325745	4-EtO-Ph	C ₂₁ H ₁₈ N ₄ OS
325747	3-thienyl	C ₁₇ H ₁₂ N ₄ S ₂

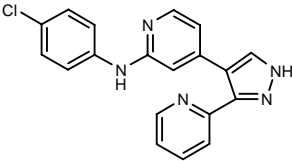
SOURCE – GlaxoSmithKline.

REFERENCES

1. Gellibert, F.J. (Glaxo Group Ltd.) *Thiazolamines and their use as TGF-β inhibitors*. WO 0262753.

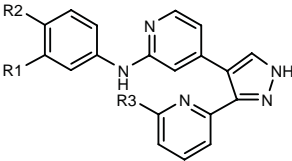
325831

N-(4-Chlorophenyl)-4-[3-(2-pyridyl)-1*H*-pyrazol-4-yl]-pyridin-2-amine



C19 H14 Cl N5; Mol wt: 347.8076

ACTION – Inhibitor of TGF-β signaling that acts by inhibiting the TGF-β type I (ALK5) receptor. When tested *in vitro* for its ability to inhibit TGF-β signaling in a luciferase reporter gene assay using HepG2 cells, compound displayed an IC₅₀ < 5 μM. It was also shown to inhibit ALK5 autophosphorylation with an IC₅₀ < 1 μM. Potentially useful for the treatment of liver and kidney fibrosis, cancer, inflammation, abnormal bone function and scarring. Other exemplified pyrazoles include the following:



Compound	R1	R2	R3	Formula
325833	H	F	H	C ₁₉ H ₁₄ FN ₅
325834	CN	H	H	C ₂₀ H ₁₄ N ₆
325835	1-pyrrolidinyl-CH2CH2O	H	H	C ₂₅ H ₂₆ N ₆ O
325836	H	1-pyrrolidinyl-CH2CH2O	H	C ₂₅ H ₂₆ N ₆ O
325837	CN	Cl	H	C ₂₀ H ₁₃ ClN ₆
325838	H	Me	H	C ₂₀ H ₁₇ N ₅
325839	H	CF3	H	C ₂₀ H ₁₄ F ₃ N ₅
325840	OMe	CN	Me	C ₂₂ H ₁₉ N ₆ O
325841	1-Me-2-imidazolyl-CH2O	H	H	C ₂₄ H ₂₁ N ₇ O

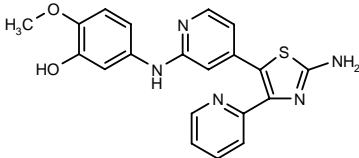
SOURCE – GlaxoSmithKline.

REFERENCES

1. Gellibert, F.J. (Glaxo Group Ltd.) *Pyrazoles as TGF inhibitors*. WO 0262787.

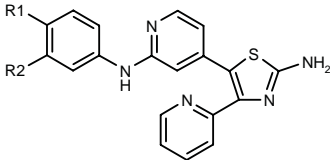
325843

5-[4-[2-Amino-4-(2-pyridyl)thiazol-5-yl]pyridin-2-ylamino]-2-methoxyphenol



C20 H17 N5 O2 S; Mol wt: 391.4533

ACTION – Inhibitor of TGF-β signaling that acts by inhibiting the TGF-β type I (ALK5) receptor. When tested *in vitro* for its ability to inhibit TGF-β signaling in a luciferase reporter gene assay using HepG2 cells, compound displayed an IC₅₀ < 5 μM. It was also shown to inhibit ALK5 autophosphorylation with an IC₅₀ < 1 μM. Potentially useful for the treatment of liver and kidney fibrosis, cancer, inflammation, abnormal bone function and scarring. Other exemplified thiazole derivatives are:



Compound	R1	R2	Formula
325844	H	CONHMe	C ₂₁ H ₁₈ N ₆ OS
325845	NHAc	H	C ₂₁ H ₁₈ N ₆ OS

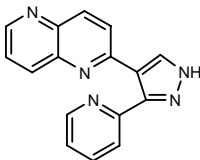
SOURCE – GlaxoSmithKline.

REFERENCES

1. Gellibert, F.J. (Glaxo Group Ltd.) *Thiazole cpds. as TGF-β inhibitors*. WO 0262793.

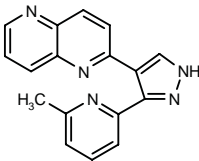
325847

2-[3-(2-Pyridyl)-1*H*-pyrazol-4-yl]-1,5-naphthyridine



C16 H11 N5; Mol wt: 273.2979

ACTION – Inhibitor of TGF-β signaling that acts by inhibiting the TGF-β type I (ALK5) receptor. When tested *in vitro* for its ability to inhibit TGF-β signaling in a luciferase reporter gene assay using HepG2 cells, compound displayed an IC₅₀ < 0.05 μM. Potentially useful for the treatment of liver and kidney fibrosis, cancer, inflammation, abnormal bone function and scarring. Another exemplified compound is:



325849: C17 H13 N5

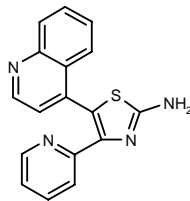
SOURCE – GlaxoSmithKline.

REFERENCES

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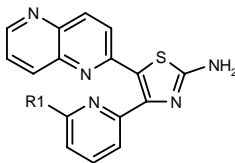
325850

4-(2-Pyridyl)-5-(4-quinoliny)thiazol-2-amine



C17 H12 N4 S; Mol wt: 304.3758

ACTION – Inhibitor of TGF-β signaling that acts by inhibiting the TGF-β type I (ALK5) receptor. When tested *in vitro* for its ability to inhibit TGF-β signaling in a luciferase reporter gene assay using HepG2 cells, compound displayed an IC₅₀ < 5 μM. It was also shown to inhibit ALK5 autophosphorylation with an IC₅₀ < 1 μM. Potentially useful for the treatment of liver and kidney fibrosis, cancer, inflammation, abnormal bone function and scarring. Other exemplified thiazole derivatives are:



Compound	R1	Formula
325851	H	C ₁₆ H ₁₁ N ₅ S
325852	Me	C ₁₇ H ₁₃ N ₅ S

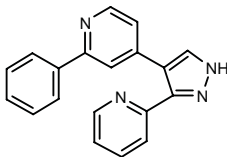
SOURCE – GlaxoSmithKline.

REFERENCES

1. Gellibert, F.J. et al. (Glaxo Group Ltd.) *2-Amino-4-(pyridin-2-yl)-thiazole derivs. as transforming growth factor β (TGF-β) inhibitors*. WO 0262776.

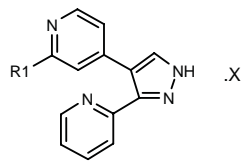
326378

2-Phenyl-4-[3-(2-pyridyl)-1*H*-pyrazol-4-yl]pyridine



C19 H14 N4; Mol wt: 298.3476

ACTION – Inhibitor of the TGF-β signaling pathway that acts by interfering with the TGF-β type I (ALK5) receptor. Potentially useful for the treatment of fibrotic conditions, particularly liver and kidney fibrosis, cancer, abnormal bone function and scarring. Other specifically claimed pyrazole derivatives are:



Compound	R1	X	Formula
326379	4-F-Ph		C ₁₉ H ₁₃ FN ₄
326380	3-thienyl		C ₁₇ H ₁₂ N ₄ S
326382	4-(4-morpholinyl)-Ph		C ₂₃ H ₂₁ N ₅ O
326383	4-[1-Pip-(CH ₂) ₂ CONH]Ph	HCl	C ₂₇ H ₂₈ N ₆ O.HCl
326384	4-[4-THP-N(Me)]-Ph		C ₂₅ H ₂₅ N ₅ O
326386	4-(4-MeO-1-Pip-CH ₂)-Ph		C ₂₆ H ₂₇ N ₅ O
326387	4-[4-[N(Me) ₂]-1-Pip-CO]-Ph		C ₂₇ H ₂₈ N ₆ O
326388	4-[CON(Me)CH ₂ CH ₂ OMe]-Ph		C ₂₄ H ₂₃ N ₅ O ₂

SOURCE – GlaxoSmithKline.

REFERENCES

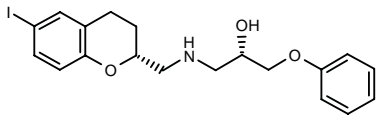
1. Gellibert, F.J. and Mathews, N. (Glaxo Group Ltd.) *Pyrazole derivs. against TGF overexpression*. WO 0266462.

ENDOCRINE DRUGS

ANTIDIABETIC DRUGS

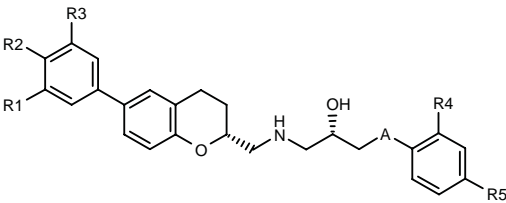
323230

1-[6-Iodo-3,4-dihydro-2H-1-benzopyran-2(R)-ylmethyl-amino]-3-phenoxypropan-2(S)-ol



C19 H22 I N O3; Mol wt: 439.2868

ACTION – β₃-Adrenoceptor agonist shown to stimulate the production of cAMP in human β₃-adrenoceptor-transfected CHO cells with an EC₅₀ < 1 μM. Potentially useful for the treatment of diabetes, impaired glucose tolerance, obesity, benign prostatic hyperplasia and hypertriglyceridemia and lipoprotein disorders, as well as other conditions mediated by β₃-adrenoceptors including gastrointestinal disorders, neurogenic inflammation, ocular hypertension, glaucoma and urinary incontinence. Other exemplified disubstituted aminomethyl chroman derivatives are:



Compound	R1	R2	R3	R4	R5	A	Formula
323231	H	CO ₂ Me	H	CF ₃	H	O	C ₂₈ H ₂₈ F ₃ NO ₅
323232	CO ₂ Et	H	H	H	H	O	C ₂₈ H ₃₁ NO ₅
323233	CO ₂ Me	-OCH ₂ CH ₂ -	H	H	H	O	C ₂₉ H ₃₁ NO ₆
323234	H	CO ₂ H	H	H	CH ₂ CH ₂ OMe	O	C ₂₉ H ₃₃ NO ₆
323235	H	CO ₂ H	H	Cl	H	O	C ₂₆ H ₂₆ ClNO ₅
323236	H	CO ₂ H	H	F	H	S	C ₂₆ H ₂₆ FNO ₄ S
323237	H	CO ₂ H	NH ₂	H	H	O	C ₂₆ H ₂₈ N ₂ O ₅
323238	4-Me-Ph	CO ₂ H	H	H	H	O	C ₃₃ H ₃₃ NO ₅

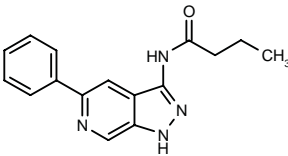
SOURCE – Bayer.

REFERENCES

1. Ladouceur, G.H. et al. (Bayer Corp.) *Di-substd. aminomethyl chroman deriv. β₃ adrenoreceptor agonists*. WO 0248134.

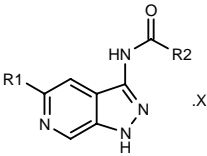
323323

N-(5-Phenyl-1H-pyrazolo[3,4-c]pyridin-3-yl)butyramide



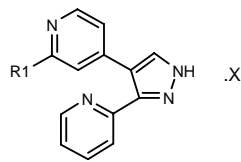
C16 H16 N4 O; Mol wt: 280.3294

ACTION – Potent and selective inhibitor of glycogen synthase kinase-3 (GSK-3), potentially useful for the treatment of diabetes and diabetic complications, chronic neurodegenerative conditions such as Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis and multiple sclerosis, stroke, schizophrenia, bipolar disorders, hair loss, obesity, atherosclerosis, hypertension, polycystic ovary syndrome, cancer, inflammation and immunodeficiency, among other GSK-3-mediated conditions. Other exemplified pyrazolo-[3,4-c]pyridines are:



Compound	R1	R2	X	Formula
323324	2,3-(F)2-Ph	i-Pr		C ₁₆ H ₁₄ F ₂ N ₄ O
323325	2,3-(F)2-Ph	1-Me-4-Pip	HCl	C ₁₉ H ₁₉ F ₂ N ₅ O.HCl
323326	6-Me-3-Pyr	cyclopropyl		C ₁₆ H ₁₅ N ₅ O
323327	Ph	1-Pip-(CH ₂) ₃	tartrate	C ₂₁ H ₂₅ N ₅ O.C ₄ H ₆ O ₆

ACTION – Inhibitor of the TGF-β signaling pathway that acts by interfering with the TGF-β type I (ALK5) receptor. Potentially useful for the treatment of fibrotic conditions, particularly liver and kidney fibrosis, cancer, abnormal bone function and scarring. Other specifically claimed pyrazole derivatives are:



Compound	R1	X	Formula
326379	4-F-Ph		C ₁₉ H ₁₃ FN ₄
326380	3-thienyl		C ₁₇ H ₁₂ N ₄ S
326382	4-(4-morpholinyl)-Ph		C ₂₃ H ₂₁ N ₅ O
326383	4-[1-Pip-(CH ₂) ₂ CONH]Ph	HCl	C ₂₇ H ₂₈ N ₆ O.HCl
326384	4-[4-THP-N(Me)]-Ph		C ₂₅ H ₂₅ N ₅ O
326386	4-(4-MeO-1-Pip-CH ₂)-Ph		C ₂₆ H ₂₇ N ₅ O
326387	4-[4-[N(Me) ₂]-1-Pip-CO]-Ph		C ₂₇ H ₂₈ N ₆ O
326388	4-[CON(Me)CH ₂ CH ₂ OMe]-Ph		C ₂₄ H ₂₃ N ₅ O ₂

SOURCE – GlaxoSmithKline.

REFERENCES

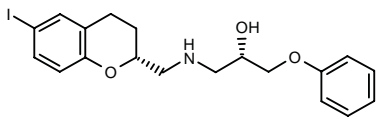
1. Gellibert, F.J. and Mathews, N. (Glaxo Group Ltd.) *Pyrazole derivs. against TGF overexpression*. WO 0266462.

ENDOCRINE DRUGS

ANTIDIABETIC DRUGS

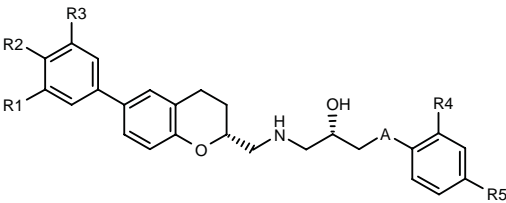
323230

1-[6-Iodo-3,4-dihydro-2H-1-benzopyran-2(R)-ylmethyl-amino]-3-phenoxypropan-2(S)-ol



C19 H22 I N O3; Mol wt: 439.2868

ACTION – β₃-Adrenoceptor agonist shown to stimulate the production of cAMP in human β₃-adrenoceptor-transfected CHO cells with an EC₅₀ < 1 μM. Potentially useful for the treatment of diabetes, impaired glucose tolerance, obesity, benign prostatic hyperplasia and hypertriglyceridemia and lipoprotein disorders, as well as other conditions mediated by β₃-adrenoceptors including gastrointestinal disorders, neurogenic inflammation, ocular hypertension, glaucoma and urinary incontinence. Other exemplified disubstituted aminomethyl chroman derivatives are:



Compound	R1	R2	R3	R4	R5	A	Formula
323231	H	CO ₂ Me	H	CF ₃	H	O	C ₂₈ H ₂₈ F ₃ NO ₅
323232	CO ₂ Et	H	H	H	H	O	C ₂₈ H ₃₁ NO ₅
323233	CO ₂ Me	-OCH ₂ CH ₂ -	H	H	H	O	C ₂₉ H ₃₁ NO ₆
323234	H	CO ₂ H	H	H	CH ₂ CH ₂ OMe	O	C ₂₉ H ₃₃ NO ₆
323235	H	CO ₂ H	H	Cl	H	O	C ₂₆ H ₂₆ ClNO ₅
323236	H	CO ₂ H	H	F	H	S	C ₂₆ H ₂₆ FNO ₄ S
323237	H	CO ₂ H	NH ₂	H	H	O	C ₂₆ H ₂₈ N ₂ O ₅
323238	4-Me-Ph	CO ₂ H	H	H	H	O	C ₃₃ H ₃₃ NO ₅

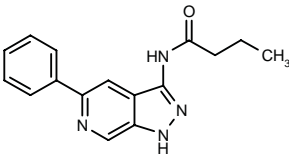
SOURCE – Bayer.

REFERENCES

1. Ladouceur, G.H. et al. (Bayer Corp.) *Di-substd. aminomethyl chroman deriv. β₃ adrenoreceptor agonists*. WO 0248134.

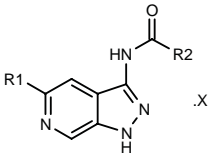
323323

N-(5-Phenyl-1H-pyrazolo[3,4-c]pyridin-3-yl)butyramide



C16 H16 N4 O; Mol wt: 280.3294

ACTION – Potent and selective inhibitor of glycogen synthase kinase-3 (GSK-3), potentially useful for the treatment of diabetes and diabetic complications, chronic neurodegenerative conditions such as Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis and multiple sclerosis, stroke, schizophrenia, bipolar disorders, hair loss, obesity, atherosclerosis, hypertension, polycystic ovary syndrome, cancer, inflammation and immunodeficiency, among other GSK-3-mediated conditions. Other exemplified pyrazolo-[3,4-c]pyridines are:



Compound	R1	R2	X	Formula
323324	2,3-(F)2-Ph	i-Pr		C ₁₆ H ₁₄ F ₂ N ₄ O
323325	2,3-(F)2-Ph	1-Me-4-Pip	HCl	C ₁₉ H ₁₉ F ₂ N ₅ O.HCl
323326	6-Me-3-Pyr	cyclopropyl		C ₁₆ H ₁₅ N ₅ O
323327	Ph	1-Pip-(CH ₂) ₃	tartrate	C ₂₁ H ₂₅ N ₅ O.C ₄ H ₆ O ₆

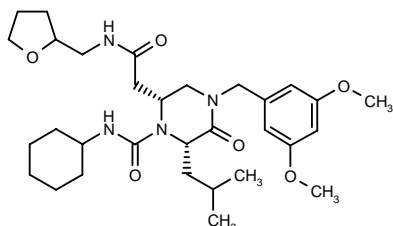
SOURCE – GlaxoSmithKline.

REFERENCES

1. Rawlings, D.A. and Witherington, J. (SmithKline Beecham plc) *Pyrazolo[3,4-c]pyridines as GSK-3 inhibitors*. WO 0250073.

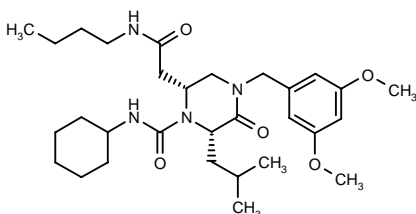
324120

N-Cyclohexyl-4-(3,5-dimethoxybenzyl)-2(*S*)-isobutyl-3-oxo-6(*R*)-[*N*-(tetrahydrofuran-2-ylmethyl)carbamoylmethyl]piperazine-1-carboxamide



C31 H48 N4 O6; Mol wt: 572.7422

ACTION – Selective peroxisome proliferator-activated receptor PPAR γ agonist reported to reduce serum glucose and insulin levels in *db/db* mice. Potentially useful for the treatment of diabetes. Another related compound is:



324121: C30 H48 N4 O5

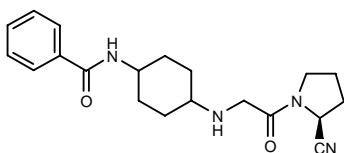
SOURCE – Advanced SynTech.

REFERENCES

1. Lou, B. and Majjli, A.M.M. (Advanced SynTech, Inc.) *Heterocycle derivs. as PPAR γ agonists*. WO 0253546.

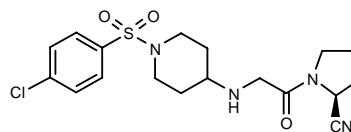
325245

N-[4-[2-[2(*S*)-Cyanopyrrolidin-1-yl]-2-oxoethylamino]-cyclohexyl]benzamide

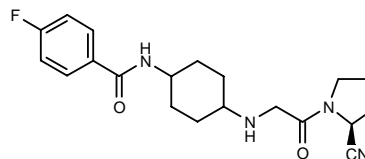


C20 H26 N4 O2; Mol wt: 354.4514

ACTION – Dipeptidyl-peptidase IV (DPP-IV) inhibitor, as demonstrated in Caco-2 cells, human plasma and rat plasma (IC₅₀ = 5, 10 and 5 nM, respectively). *In vivo*, it inhibited DPP-IV by 80% following administration to glucose-challenged rats at 10 μ mol/kg p.o. Potentially useful for the treatment of type 2 (non-insulin-dependent) diabetes. Other exemplified cyanopyrrolidines are:



325246: C18 H23 Cl N4 O3 S



325247: C20 H25 F N4 O2

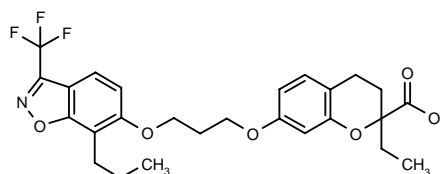
SOURCE – Novartis.

REFERENCES

1. Villhauer, E.B. (Novartis AG) *N*-(Substd. glycylyl)-2-cyanopyrrolidines, pharmaceutical compsns. containing them and their use in inhibiting dipeptidyl peptidase-IV. US 6432969, WO 0196295.

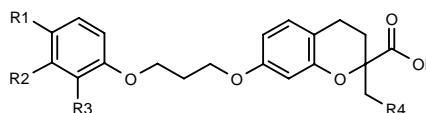
325428

2-Ethyl-7-[3-[7-propyl-3-(trifluoromethyl)-1,2-benzisoxazol-6-yloxy]propoxy]-3,4-dihydro-2*H*-1-benzopyran-2-carboxylic acid



C26 H28 F3 N O6; Mol wt: 507.5022

ACTION – Peroxisome proliferator-activated PPAR α and/or PPAR γ receptor agonist, potentially useful for the treatment of type 2 diabetes, hyperglycemia, obesity, atherosclerosis, cachexia and lipid disorders including hypercholesterolemia, hypertriglyceridemia and dyslipidemia. Other exemplified benzopyrancarboxylic acid derivatives include the following:



Compound	R1	R2	R3	R4	Isomer	Formula
325429	-C(t-BuCH2)=NO-		Pr	Me		C ₃₀ H ₂₈ NO ₆
325430	3-benzisoxazolyl	H	Pr	Me		C ₃₁ H ₃₃ NO ₆
325431	OCH2CF3	H	Cl	Et		C ₂₄ H ₂₆ ClF ₃ O ₆
325432	cyclohexyl	H	Cl	Me		C ₂₇ H ₃₃ ClO ₅
325433	i-Pr	H	Cl	Me	R	C ₂₄ H ₂₉ ClO ₅
325434	OCF3	H	Cl	Me	R	C ₂₂ H ₂₂ ClF ₃ O ₆
325435	cyclopentyl	H	Cl	H	R	C ₂₅ H ₂₉ ClO ₅
325437	4-THP	H	Cl	H	R	C ₂₅ H ₂₉ ClO ₆

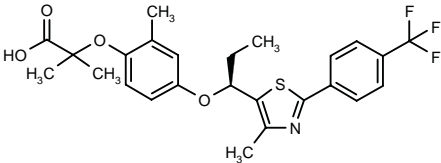
SOURCE – Merck & Co.

REFERENCES

1. Sahoo, S.P. et al. (Merck & Co., Inc.) *Benzopyrancarboxylic acid derivs. for the treatment of diabetes and lipid disorders.* WO 0260434.

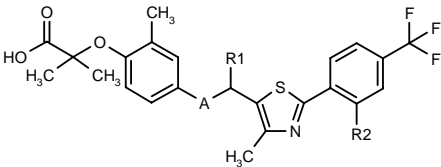
325628

2-Methyl-2-[2-methyl-4-[1 (S)-[4-methyl-2-[4-(trifluoromethyl)phenyl]thiazol-5-yl]propoxy]phenoxy]propionic acid



C25 H26 F3 N O4 S; Mol wt: 493.5434

ACTION – Peroxisome proliferator-activated receptor (PPAR) agonist giving EC₅₀ values of 5, 1.7 and 660 nM, respectively, at human PPAR α , PPAR δ and PPAR γ receptors. Potentially useful for the treatment of dyslipidemia, syndrome X, heart failure, hypercholesterolemia, cardiovascular disease, type 1 and type 2 diabetes, insulin resistance, hyperlipidemia, obesity, bulimia and anorexia nervosa. Other exemplified thiazole derivatives are:



Compound	R1	R2	A	Isomer	Formula
325629	H	F	S		C ₂₃ H ₂₁ F ₄ NO ₃ S ₂
325630	Me	H	O	S	C ₂₄ H ₂₄ F ₃ NO ₄ S
325631	Me	H	O	R	C ₂₄ H ₂₄ F ₃ NO ₄ S
325632	Et	H	O	R	C ₂₅ H ₂₆ F ₃ NO ₄ S

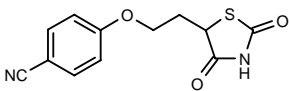
SOURCE – GlaxoSmithKline.

REFERENCES

1. Cadilla, R. et al. (Glaxo Group Ltd.) *Thiazole derivs. for treating PPAR related disorders.* WO 0262774.

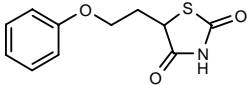
325867

4-[2-(2,4-Dioxothiazolidin-5-yl)ethoxy]benzonitrile



C12 H10 N2 O3 S; Mol wt: 262.2880

ACTION – Agent for the treatment of diabetes and insulin resistance that was shown to reduce glycemia and insulinemia by 26 and 49%, respectively, following administration to non-insulin-dependent diabetic rats at an oral dose of 200 mg/kg. Another specifically claimed thiazolidine-2,4-dione derivative is:



325870: C11 H11 N O3 S

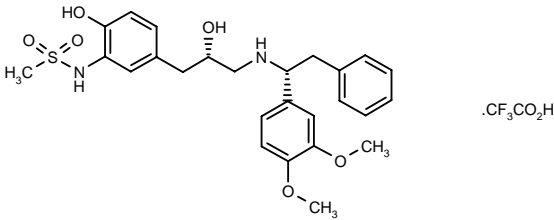
SOURCE – Merck KGaA.

REFERENCES

1. Moinet, G. et al. (Merck Patent GmbH) *Thiazolidone-2 derivs., 4-diketone substd., method for obtaining them and pharmaceutical compsns. containing same.* FR 2749583, US 2001007875, US 6437143, WO 9747612.

325901

N-[5-[3-[1 (R)-(3,4-Dimethoxyphenyl)-2-phenylethyl-amino]-2 (S)-hydroxypropyl]-2-hydroxyphenyl]methanesulfonamide trifluoroacetate



C26 H32 N2 O6 S . C2 H F3 O2; Mol wt: 614.6347

ACTION – A representative compound from a series of (4-hydroxy-3-sufonamidophenyl)propylamines that acts as a selective β_3 -adrenoceptor agonist and is therefore potentially useful for the treatment of diabetes, obesity, depression, achalasia and intestinal hypermotility disorders.

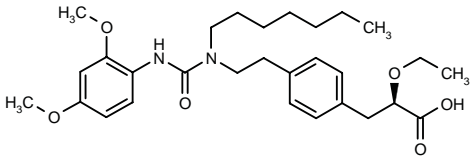
SOURCE – Bristol-Myers Squibb.

REFERENCES

1. Sher, P.M. et al. (Bristol-Myers Squibb Co.) *2-Hydroxy-3-(4-hydroxy-3-sulfonamidophenyl)-propylamines useful as beta 3 adrenergic agonists.* US 2002026065, US 6436914.

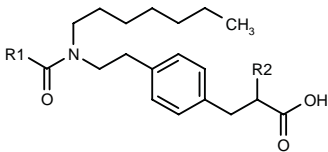
325956

3-[4-[2-[3-(2,4-Dimethoxyphenyl)-1-heptylureido]ethyl]-phenyl]-2 (R)-ethoxypropionic acid



C29 H42 N2 O6; Mol wt: 514.6588

ACTION – Peroxisome proliferator-activated PPAR α receptor agonist for the treatment of obesity, hypertriglyceridemia, hyperlipidemia and hypercholesterolemia, syndrome X, type 1 and type 2 diabetes, hyperinsulinemia, impaired glucose tolerance, insulin resistance, diabetic complications, atherosclerosis, hypertension, coronary heart disease, inflammation, thrombosis and congestive heart failure. Other exemplified compounds include the following:



Compound	R1	R2	Isomer	Formula
325957	2,3-(Cl)2-PhNH	OEt	R	C ₂₇ H ₃₆ Cl ₂ N ₂ O ₄
325959	2,3-(Cl)2-PhNH	OEt	S	C ₂₇ H ₃₆ Cl ₂ N ₂ O ₄
325960	2,4-(Me)2-PhNH	OEt	R	C ₂₉ H ₄₂ N ₂ O ₄
325961	2,4-(F)2-PhCH2	OEt	R	C ₂₈ H ₃₇ F ₂ N ₂ O ₄
325962	4-i-Pr-PhNH	OPh	R	C ₃₄ H ₄₄ N ₂ O ₄
325963	2,4-(MeO)2-PhNH	OCH2Ph	S	C ₃₄ H ₄₄ N ₂ O ₆
325964	4-i-Pr-PhNH	i-PrS	S	C ₃₁ H ₄₆ N ₂ O ₃ S
325966	4-i-Pr-PhNH	SPh	S	C ₃₄ H ₄₄ N ₂ O ₃ S

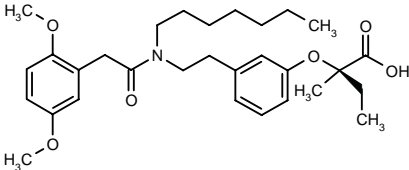
SOURCE – Pfizer.

REFERENCES

1. Hayward, C.M. and Perry, D.A. (Pfizer Products Inc.) *PPAR agonists*. WO 0264549.

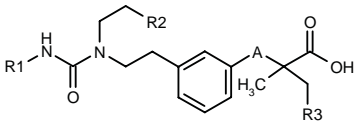
325970

2 (*R*)-[3-[2-[*N*-[2-(2,5-Dimethoxyphenyl)acetyl]-*N*-heptylamino]ethyl]phenoxy]-2-methylbutyric acid



C30 H43 N O6; Mol wt: 513.6707

ACTION – Peroxisome proliferator-activated receptor PPARα agonist, potentially useful for the treatment of obesity, hypertriglyceridemia, hyperlipidemia and hypercholesterolemia, syndrome X, type 1 and type 2 diabetes, hyperinsulinemia, impaired glucose tolerance, insulin resistance, diabetic complications, atherosclerosis, hypertension, coronary heart disease, inflammation, thrombosis and congestive heart failure. Other exemplified compounds are:



Compound	R1	R2	R3	A	Isomer	Formula
325971	4-Et-Ph	C5H11	Me	O	R	C ₂₉ H ₄₂ N ₂ O ₄
325972	4-Et-Ph	C5H11	Me	O	S	C ₂₉ H ₄₂ N ₂ O ₄
325973	4-(CF3O)-Ph	C5H11	Me	O	S	C ₂₈ H ₃₇ F ₃ N ₂ O ₅
325975	4-i-Pr-Ph	C5H11	Me	O	R	C ₃₀ H ₄₄ N ₂ O ₄
325976	4-i-Pr-Ph	C5H11	H	S		C ₂₉ H ₄₂ N ₂ O ₃ S
325978	2,4-(MeO)2-Ph	C5H11	H	S		C ₂₈ H ₄₀ N ₂ O ₅ S
325982	C5H11	2,4-(F)2-Ph	Me	O	S	C ₂₇ H ₃₆ F ₂ N ₂ O ₄
325984	C6H13	2,4-(F)2-Ph	Me	O	S	C ₂₈ H ₃₈ F ₂ N ₂ O ₄

SOURCE – Pfizer.

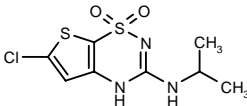
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NNC-55-0118

264270

6-Chloro-*N*-isopropyl-4*H*-thieno[3,2-*e*][1,2,4]thiadiazin-3-amine 1,1-dioxide



C8 H10 Cl N3 O2 S2; Mol wt: 279.7710

ACTION – Potent and selective activator of the ATP-sensitive potassium (K_{ATP}) channel shown to inhibit [³H]-glibenclamide binding in HEK293 cells expressing human SUR1/Kir6.2 channels with an IC₅₀ of 0.34 μM in the presence of high concentrations of MgATP. It inhibited glucose-stimulated insulin release from rat islets with an IC₅₀ of 0.18 μM, but was much less active in relaxing KCl-contracted rat aortic rings (EC₅₀ = 266.0 μM) and mesenteric arteries (EC₅₀ = 6.2 μM). In normal rats, 30 mg/kg p.o. reduced both resting and glucose-stimulated plasma insulin levels for up to 6 h, without inducing resting hyperglycemia and with minimal effects on cardiovascular parameters. Moreover, compound protected β-cells against the toxic effects of streptozotocin and prevented the development of type 2 diabetes in a genetic rat model of obesity and diabetes.

SOURCE – Novo Nordisk.

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1. Ebdrup, S. and Nielsen, F.E. (Novo Nordisk A/S) *Novel process*. WO 0102410.

2. Hansen, J.B. (Novo Nordisk A/S) *Use of potassium channel agonists for the treatment of cancer*. WO 0200222.

3. Hansen, J.B. and Bjenning, C. (Novo Nordisk A/S) *Use of potassium channel agonists for reducing fat food consumption*. WO 0200223.

4. Hansen, J.B. et al. (Novo Nordisk A/S) *Use of potassium channel openers for the treatment of insulinitis*. WO 0200665.

5. Nielsen, F.E. et al. (Novo Nordisk A/S) *A new process for preparing fused 1,2,4-thiadiazine derivs*. WO 0250085.

6. Nielsen, F.E. et al. (Novo Nordisk A/S) *Fused 1,2,4-thiadiazine and fused 1,4-thiazine derivs., their preparation and use*. EP 0876379, JP 1998508881, US 5889002, WO 9726265.

7. Nielsen, F.E. et al. (Novo Nordisk A/S) *Fused 1,2,4-thiadiazine derivs., their preparation and use*. EP 1000066, JP 2001510195, WO 9903861.

8. Bjenning, C. et al. *Potassium channel agonists profoundly reduce snacking in the obese Zucker rat*. Obes Res 2000, 8(Suppl. 1): Abst PE12.

9. Kullin, M. et al. *K_{ATP} channel openers protect rat islets against the toxic effect of streptozotocin*. Diabetes 2000, 49(7): 1131.

10. Kullin, M. et al. *Protection against nitric oxide by potassium channel openers*. 5th Int Congr Immunol Diabetes Soc (Feb 14-16, Chennai) 2001, Abst 23.

11. Nielsen, F.E. et al. *6-Chloro-3-alkylamino-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide derivatives potently and selectively activate ATP sensitive potassium channels of pancreatic β -cells*. J Med Chem 2002, 45(19): 4171.

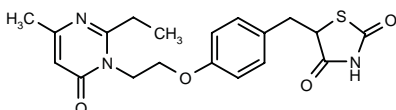
12. Rasmussen, S.B. et al. *Functional rest through intensive treatment with insulin and potassium channel openers preserves residual β -cell function and mass in acutely diabetic BB rats*. Horm Metab Res 2000, 32(7): 294.

13. *Annual Report: Novo Nordisk*. DailyDrugNews.com (Daily Essentials) 1998, May 6.

PMT-13*

274470

5-[4-[2-(2-Ethyl-4-methyl-6-oxo-1,6-dihydro-1-pyrimidin-yl)ethoxy]benzyl]thiazolidine-2,4-dione



C19 H21 N3 O4 S; Mol wt: 387.4579

ACTION – Antidiabetic agent proven to selectively activate the peroxisome proliferator-activated receptor PPAR γ with similar potency to rosiglitazone (K_D = 430 and 482 nM, respectively, in a transactivation assay). In insulin-resistant *db/db* mice, compound (10 mg/kg/day p.o.) reduced plasma glucose, triglyceride and insulin levels by 72, 59 and 77%, respectively, compared to respective reductions of 47, 41 and 42% for rosiglitazone. In the *ob/ob* mouse model, the same dose level reduced plasma glucose and triglyceride levels by 71 and 51%, respectively, compared to respective reductions of 77 and 38% for rosiglitazone; in this model, both compounds similarly decreased plasma insulin levels. In Zucker rats, PMT-13 (3 mg/kg/day p.o.) was more effective than the reference compound in reducing plasma triglyceride, free fatty acid and insulin levels, with respective reductions of 51% versus 34%, 69% versus 44% and 68% versus 46%. Compound also inhibited liver glucose-6-phosphatase and increased lipoprotein lipase activity. No toxicity or treatment-related side effects were seen in 28-day toxicity studies in mice.

SOURCE – Dr. Reddy's Research Foundation.

REFERENCES

1. Lohray, V.B. et al. (Dr. Reddy's Research Foundation) *Heterocyclic cpds., process for their preparation and pharmaceutical compsns. containing them and their use in the treatment of diabetes and related diseases*. EP 0958296, US 5885997, US 5985884, US 6372750, WO 9741097.

2. Chakrabarti, R. et al. *Antidiabetic and hypolipidemic potential of PMT13, a pyrimidine analogue of thiazolidinedione*. Diabetes Mellit: Mol Mech Genet Prospect New Ther (Feb 16-22, Taos) 2000, Abst 408.

3. Chakrabarti, R. et al. *PMT13, a pyrimidine analogue of thiazolidinedione improves insulin resistance-associated disorders in animal models of type 2 diabetes*. Diabetes Obes Metab 2002, 4(5): 319.

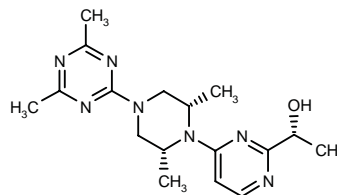
4. Madhavan, G.R. et al. *Synthesis and biological activity of novel pyrimidinone containing thiazolidinedione derivatives*. Bioorg Med Chem 2002, 10(8): 2671.

*Identified compound 274470 (see 274461) Drug Data Rep 1999, 021(05): 0428.

TREATMENT OF DIABETIC COMPLICATIONS

325353

1-(*R*)-[4-[4-(4,6-Dimethyl-1,3,5-triazin-2-yl)-2(*R*),6(*S*)-dimethylpiperazin-1-yl]pyrimidin-2-yl]ethanol



C17 H25 N7 O; Mol wt: 343.4325

ACTION – Potent, orally active sorbitol dehydrogenase (L-iditol 2-dehydrogenase) inhibitor (IC_{50} = 4 and 5 nM against rat and human enzyme, respectively) with high selectivity (> 2,500-fold) over other dehydrogenases. *In vivo*, a dose of 50 mg/kg p.o. produced long-lasting (24 h) normalization of elevated sciatic nerve fructose levels in rats with chronic streptozotocin-induced diabetes. It also exhibited favorable pharmaceutical properties including good lipophilicity and solubility in stimulated gastric fluid, as well as low plasma protein binding and metabolic stability. Potentially useful for the treatment of diabetic complications.

SOURCE – Pfizer.

REFERENCES

1. Chu-Moyer, M.Y. et al. (Pfizer Products Inc.) *Aminopyrimidines as sorbitol dehydrogenase inhibitors*. EP 1185275, US 6414149, WO 0059510.

2. Mylari, B.L. (Pfizer Products Inc.) *Combination of GABA agonists and sorbitol dehydrogenase inhibitors*. WO 0243762.

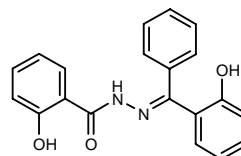
3. Mylari, B.L. (Pfizer Products Inc.) *Combination of statins and sorbitol dehydrogenase inhibitors*. WO 0232411.

4. Mylari, B.L. *Salts of zopolrestat*. US 2001056095.

5. Mylari, B.L. et al. *A sorbitol dehydrogenase inhibitor of exceptional in vivo potency with a long duration of action: 1-(R)-[4-[4-(4,6-Dimethyl[1,3,5]triazin-2-yl)-2R,6S-dimethylpiperazin-1-yl]pyrimidin-2-yl]ethanol*. J Med Chem 2002, 45(20): 4398.

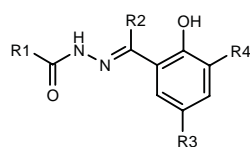
325940

2-Hydroxy-*N'*-[1-(2-hydroxyphenyl)-1-phenylmethylenidene]benzohydrazide



C20 H16 N2 O3; Mol wt: 332.3574

ACTION – Agent with the ability to inhibit the production of advanced glycation end products (AGEs), potentially useful for the treatment of diabetic complications, as well as cataracts, arterial disorders, Alzheimer’s disease, amyotrophic lateral sclerosis, dialysis amyloidosis and rheumatoid arthritis. Compound inhibited the production of AGEs *in vitro* with IC₅₀ values of 1.6 and 18 µM, as measured in fluorescence and ELISA assays, respectively. *In vivo*, it was found to be active in a rat model of diabetic nephropathy following oral administration at a dose of 1 mg/kg/day for 4 weeks, and showed no toxicity in mice at oral doses up to 600 mg/kg/day for 2 weeks. In addition, it displayed no mutagenicity in the Ames test. Other exemplified compounds are:



Compound	R1	R2	R3	R4	Formula
325941	2-OH-Ph	CH2Ph	Me	H	C ₂₂ H ₂₀ N ₂ O ₃
325942	5-(<i>t</i> -BuOCO)-4,5,6,7-tetrahydro-thieno[3,2- <i>c</i>]pyridin-2-yl	2-OH-Ph	H	H	C ₂₆ H ₂₇ N ₃ O ₃ S
325943	2-OH-Ph	2-OH-Ph	H	H	C ₂₀ H ₁₆ N ₂ O ₄
325944	3-(MeOCH2CH2NHSO2)-Ph	2-OH-Ph	H	H	C ₂₃ H ₂₃ N ₃ O ₆ S
325945	3-[N(Et)2SO2]-Ph	CH2Ph	Me	H	C ₂₆ H ₂₉ N ₃ O ₄ S
325946	4-Pyr	CH2Ph	Me	Me	C ₂₂ H ₂₁ N ₃ O ₂

SOURCE – Meiji Seika.

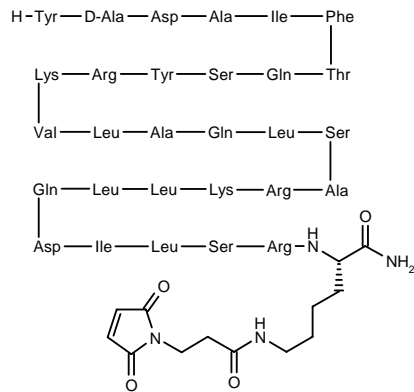
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1. Tsutsumi, S. et al. (Meiji Seika Kaisha, Ltd.) *Novel cpd. having Maillard reaction inhibitory activity.* WO 0260858.

TREATMENT OF GROWTH HORMONE SECRETION DISORDERS

325802

L-Tyrosyl-D-alanyl-L-aspartyl-L-alanyl-L-isoleucyl-L-phenylalanyl-L-threonyl-L-glutaminy-L-seryl-L-tyrosyl-L-arginyl-L-lysyl-L-valyl-L-leucyl-L-alanyl-L-glutaminy-L-leucyl-L-seryl-L-alanyl-L-arginyl-L-lysyl-L-leucyl-L-leucyl-L-glutaminy-L-aspartyl-L-isoleucyl-L-leucyl-L-seryl-L-arginyl-*N*⁶-[3-(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)propionyl]-L-lysineamide



C165 H269 N47 O46; Mol wt: 3647.2230

ACTION – Growth hormone-releasing factor (GRF) derivative containing a reactive moiety able to covalently bind to blood components, thus conferring an extended half-life *in vivo*. Compound was able to stimulate growth hormone (GH) secretion in rat primary anterior pituitary cells at 1 nM. It also demonstrated GH-releasing activity *in vivo* when administered to rats at a dose of 1 µmol/kg s.c. In pharmacokinetic studies in rats following s.c. (1 µmol/kg) and i.v. (100 nmol/kg) administration, it gave respective half-lives of 25.8 and 18.7 h, and high AUC values. Potentially useful for the treatment of pituitary dwarfism, growth retardation, bone fracture, wound healing, burns, congestive heart failure, frailty associated with aging, osteoporosis, obesity and cachexia, as well as for improving muscle strength, metabolic and renal homeostasis, and protein anabolism.

SOURCE – ConjuChem.

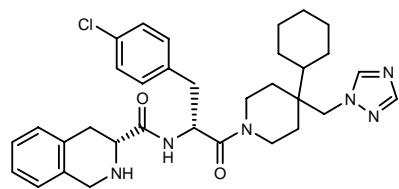
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TREATMENT OF MALE SEXUAL DYSFUNCTION

325014

N-[1(*R*)-(4-Chlorobenzyl)-2-[4-cyclohexyl-4-(1*H*-1,2,4-triazol-1-ylmethyl)piperidin-1-yl]-2-oxoethyl]-1,2,3,4-tetrahydroisoquinoline-3(*R*)-carboxamide



C33 H41 Cl N6 O2; Mol wt: 589.1799

ACTION – Potent and selective, small-molecule melanocortin MC₄ receptor agonist giving an IC₅₀ of 1.2 nM for the human receptor in binding studies and displaying > 100-fold selectivity over MC₃ and MC₅ receptors; in functional assays, it acted as a full agonist at the human MC₄ receptor (EC₅₀ = 2.1 nM for cAMP accumulation in CHO cells expressing the human receptor; 97% activation relative to α-MSH at 10 µM) and exhibited excellent functional selectivity relative to MC₃ and MC₅ receptors (EC₅₀ = 2487 and 736 nM, respectively). A good pharmacokinetic profile was observed in rats and dogs, with an oral bioavailability of 14 and 16%, respectively, rapid absorption and a short half-life. Moreover, compound significantly reduced food intake in animal models, and produced a significant and dose-dependent increase in the number of erections in rats after i.v. (ED₅₀ = 0.87 mg/kg) and oral administration (31% increase at 20 mg/kg).

SOURCE – Merck & Co.

REFERENCES

1. Bakshi, R.K. et al. (Merck & Co., Inc.) *Substd. piperidines as melanocortin-4 receptor agonists*. EP 1187614, US 6350760, WO 0074679.

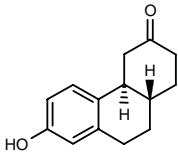
2. Sebhat, I.K. et al. *Design and pharmacology of N-[(3R)-1,2,3,4-tetrahydro-isoquinolinium-3-ylcarbonyl]-(1R)-1-(4-chlorobenzyl)-2-[4-cyclohexyl-4-(1H-1,2,4-triazol-1-ylmethyl)piperidin-1-yl]-2-oxoethylamine (1), a potent, selective, melanocortin subtype-4 receptor agonist*. J Med Chem 2002, 45(21): 4589.

3. Van der Ploeg, L.H.T. et al. *A role for the melanocortin 4 receptor in sexual function*. Proc Natl Acad Sci USA 2002, 99(17): 11381.

TREATMENT OF GYNECOLOGICAL DISORDERS

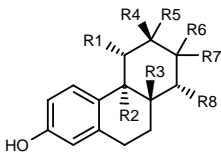
324141

(±)-(4α,10αβ)-7-Hydroxy-1,2,3,4,4a,9,10,10a-octahydro-phenanthren-3-one

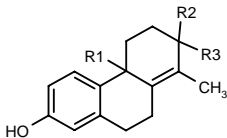


C14 H16 O2; Mol wt: 216.2784

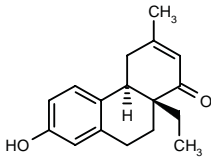
ACTION – Estrogen receptor ligand with selectivity for either the ERα or ERβ receptor subtype. Potentially useful for estrogen replacement therapy and for the treatment of estrogen-related conditions such as bone loss, osteoporosis, cartilage degeneration, endometriosis, uterine fibrosis, cardiovascular diseases, etc. Other exemplified compounds are:



Compound	R1	R2	R3	R4	R5	R6	R7	R8	Formula
324143	H	H	Me	-S(CH2)3S-		H	H	i-BuCH2	C ₂₃ H ₃₄ OS ₂
324144	H	H	Et	-O-		H	H	i-BuCH2	C ₂₁ H ₃₀ O ₂
324145	Me	H	Me	-SCH2CH2S-		H	H	H	C ₁₈ H ₂₄ OS ₂
324146	H	H	Me	-O(CH2)3-		H	H	H	C ₁₈ H ₂₄ O ₂
324149	H	Me	H	H	H	N(OH)		H	C ₁₅ H ₁₉ NO ₂



Compound	R1	R2	R3	Formula
324147	H	H	H	C ₁₅ H ₁₈ O
324148	Bu	-O-		C ₁₉ H ₂₄ O ₂



324142: C17 H20 O2

SOURCES – Karo Bio; Merck & Co.

REFERENCES

1. Koehler, K. et al. (Karo Bio AB;Merck & Co., Inc.) *Novel estrogen receptor ligands and methods I*. WO 0253522.

ENJUVIA™

326277

Plant-derived conjugated estrogen containing 10 essential active estrogenic components including Δ^{8,9}-dehydro-estrone sulfate

ACTION – Synthetic, plant-derived, modified-release conjugated estrogens, currently under review by the FDA for the treatment of vasomotor symptoms in postmenopausal women. Results of a double-blind, multicenter phase III study in postmenopausal women with at least 50 moderate to severe hot flushes per week showed that compound was safe and well tolerated, and significantly decreased both the number and severity of flushes experienced by the patients.

SOURCE – Endeavor Pharmaceuticals.

REFERENCES

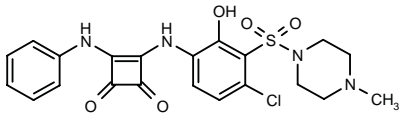
1. Utian, W.H. et al. *Efficacy and safety study of a new synthetic 10-component, modified release conjugated estrogens (CE) tablet for treatment of vasomotor symptoms in postmenopausal women*. Fertil Steril 2002, 76(3, Suppl. 1): Abst P-129.

DERMATOLOGIC DRUGS

ANTIPSORIATICS

324713

3-[4-Chloro-2-hydroxy-3-(4-methylpiperazin-1-ylsulfonyl)phenylamino]-4-(phenylamino)-3-cyclobutene-1,2-dione



C21 H21 Cl N4 O5 S; Mol wt: 476.9389

SOURCE – Merck & Co.

REFERENCES

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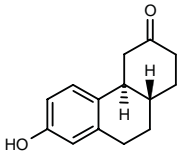
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TREATMENT OF GYNECOLOGICAL DISORDERS

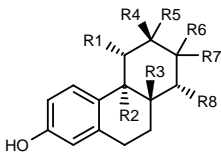
324141

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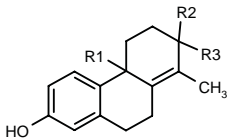


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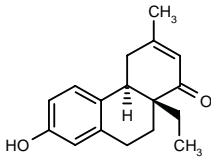
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324143	H	H	Me	-S(CH2)3S-		H	H	i-BuCH2	C ₂₃ H ₃₄ OS ₂
324144	H	H	Et	-O-		H	H	i-BuCH2	C ₂₁ H ₃₀ O ₂
324145	Me	H	Me	-SCH2CH2S-		H	H	H	C ₁₈ H ₂₄ OS ₂
324146	H	H	Me	-O(CH2)3-		H	H	H	C ₁₈ H ₂₄ O ₂
324149	H	Me	H	H	H	N(OH)		H	C ₁₅ H ₁₉ NO ₂



Compound	R1	R2	R3	Formula
324147	H	H	H	C ₁₅ H ₁₈ O
324148	Bu	-O-		C ₁₉ H ₂₄ O ₂



324142: C17 H20 O2

SOURCES – Karo Bio; Merck & Co.

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SOURCE – Endeavor Pharmaceuticals.

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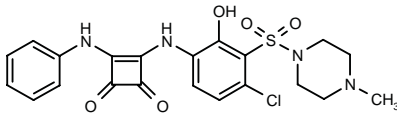
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DERMATOLOGIC DRUGS

ANTIPSORIATICS

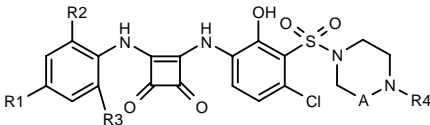
324713

3-[4-Chloro-2-hydroxy-3-(4-methylpiperazin-1-ylsulfonyl)phenylamino]-4-(phenylamino)-3-cyclobutene-1,2-dione



C21 H21 Cl N4 O5 S; Mol wt: 476.9389

ACTION – Agent with the ability to inhibit the binding of IL-8 to its receptors (CXCR1, CXCR2), as demonstrated *in vitro* in hamster ovary preparations. Potentially useful for the treatment of a broad range of IL-8-mediated disorders such as psoriasis, atopic dermatitis, arthritis, asthma, chronic obstructive pulmonary disease, inflammatory bowel disease, stroke, septic shock, multiple sclerosis, glomerulonephritis, thrombosis, transplant rejection, Alzheimer’s disease, restenosis, atherosclerosis or osteoporosis. Other exemplified compounds are:



Compound	R1	R2	R3	R4	A	Formula
324716	H	Br	H	Me	-CH2-	C ₂₁ H ₂₀ BrClN ₄ O ₅ S
324718	H	Cl	H	Me	-CH2-	C ₂₁ H ₂₀ Cl ₂ N ₄ O ₅ S
324719	H	OMe	H	Me	-CH2-	C ₂₂ H ₂₃ ClN ₄ O ₆ S
324720	H	F	H	Me	-CH2-	C ₂₁ H ₂₀ ClFN ₄ O ₅ S
324721	F	H	H	Me	-CH2-	C ₂₁ H ₂₀ ClFN ₄ O ₅ S
324722	H	F	F	Me	-CH2-	C ₂₁ H ₁₉ ClF ₂ N ₄ O ₅ S
324723	F	F	H	Me	-CH2-	C ₂₁ H ₁₉ ClF ₂ N ₄ O ₅ S
324724	F	Cl	H	Me	-CH2-	C ₂₁ H ₁₉ Cl ₂ FN ₄ O ₅ S
324725	H	H	H	H	-CH2-	C ₂₀ H ₁₉ ClN ₄ O ₅ S
324726	H	H	H	Me	-(CH2)2-	C ₂₂ H ₂₃ ClN ₄ O ₅ S
324727	H	Cl	H	Me	-(CH2)2-	C ₂₂ H ₂₂ Cl ₂ N ₄ O ₅ S

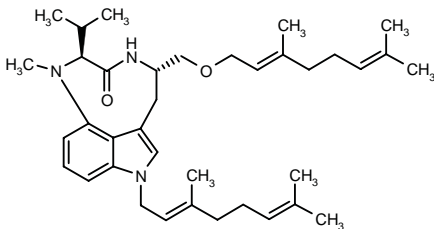
SOURCE – GlaxoSmithKline.

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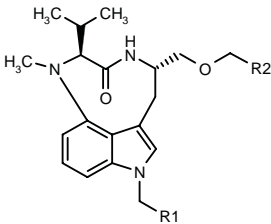
325902

8-(3,7-Dimethylocta-2,6-dienyl)-5(*S*)-(3,7-dimethylocta-2,6-dienyloxymethyl)-2(*S*)-isopropyl-1-methyl-2,3,4,5,6,8-hexahydro-1*H*-[1,4]diazonino[7,6,5-*cd*]indol-3-one



C37 H55 N3 O2; Mol wt: 573.8605

ACTION – Protein kinase C (PKC) modulator, potentially useful for the treatment of inflammation and psoriasis, among other PKC-mediated disorders. Other specifically claimed compounds are:



Compound	R1	R2	Formula
325903	C7H15	C7H15	C ₃₃ H ₅₅ N ₃ O ₂
325904	CH=CHPh	CH=CHPh	C ₃₅ H ₃₉ N ₃ O ₂

SOURCE – Procyon.

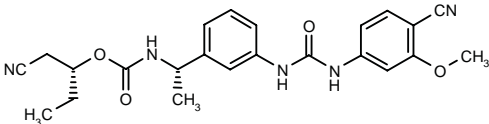
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VX-148*

295178

N-[1(*S*)-[3-[3-(4-Cyano-3-methoxyphenyl)ureido]phenyl]-ethyl]carbamic acid 1(*R*)-(cyanomethyl)propyl ester



C23 H25 N5 O4; Mol wt: 435.4815

ACTION – Immunosuppressant, a potent uncompetitive inhibitor of inosine 5'-monophosphate (IMP) dehydrogenase (K_i = 14 and 6 nM against type I and II enzyme, respectively) with high selectivity over other dehydrogenases including NAD and NADPH. *In vitro*, it inhibited the proliferation of human peripheral blood mononuclear cells stimulated with T- or B-cell mitogens (IC_{50} = 82 and 73 nM, respectively); the addition of guanosine to the cell culture blocked the inhibitory effects of compound. It also inhibited the proliferation of lymphocytes obtained from rats and mice, as well as immortalized lymphoid and myeloid cells, but it did not stimulate the proliferation of other cell types such as fibroblasts. In a murine model of primary antibody production in response to antigenic stimulation, oral treatment with compound beginning just after immunization with sheep red blood cells significantly reduced plaque formation with an ED_{50} of 38 mg/kg. It also significantly prolonged skin graft survival in mice in a dose-dependent manner. Currently in phase I clinical trials for the treatment of psoriasis.

SOURCE – Vertex.

REFERENCES

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7. *Vertex offers progress report for first half of 2002.* DailyDrugNews.com (Daily Essentials) 2002, July 24.
8. *Vertex reports Q1 2001 results.* DailyDrugNews.com (Daily Essentials) 2001, April 30.
9. *Vertex updates its progress and plans for 2002.* DailyDrugNews.com (Daily Essentials) 2002, Jan 15.
10. *Vertex updates latest R&D progress.* DailyDrugNews.com (Daily Essentials) 2002, Nov 22.
11. *VX-148 enters clinical development.* DailyDrugNews.com (Daily Essentials) 2000, Dec 22.

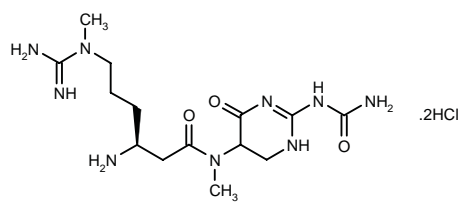
*Identified compound **295178** (see **295175**) Drug Data Rep 2001, 023(02): 0173.

ANTIINFECTIVE THERAPY

ANTIBIOTICS

324612

3(S)-Amino-*N*-methyl-6-(1-methylguanidino)-*N*-(4-oxo-2-ureido-1,4,5,6-tetrahydropyrimidin-5-yl)hexanamide dihydrochloride



C14 H27 N9 O3 . 2HCl; Mol wt: 442.3491

ACTION – Antibiotic derived from the natural compound TAN-1057 that acts by inhibiting bacterial translation (IC₅₀ = 0.06 μM) and is active against Gram-positive pathogens including *Staphylococcus aureus*, *Staphylococcus epidermidis* and *Streptococcus pyogenes* (MIC = 0.025, 0.12 and 0.5 μg/ml, respectively). *In vivo*, compound protected mice from systemic infections produced by *S. aureus* with an ED₁₀₀ < 0.5 mg/kg i.v.

SOURCE – Bayer.

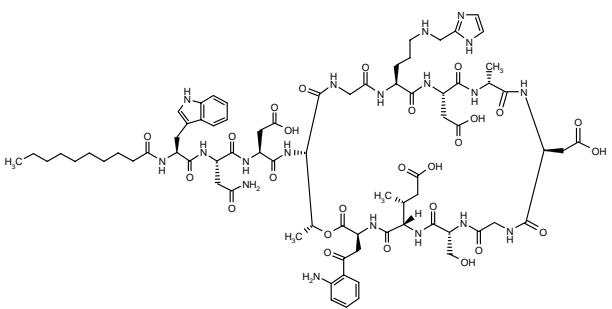
REFERENCES

1. Brands, M. et al. (Bayer AG) *TAN-1057 derivs.* DE 19838998, EP 1117652, JP 2002523496, WO 0012484.

2. Brands, M. et al. *Novel antibiotics for the treatment of Gram-positive bacterial infections.* J Med Chem 2002, 45(19): 4246.

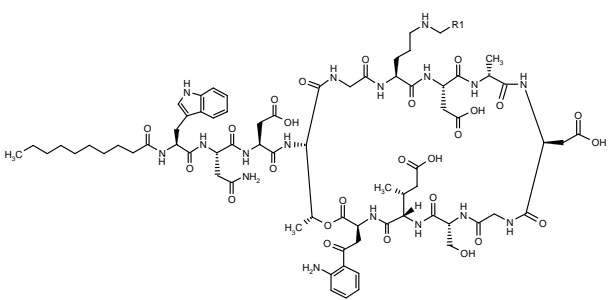
325711

N-Decanoyl-L-tryptophyl-L-asparaginyl-L-aspartyl-L-threonyl-glycyl-*N*⁵-(1*H*-imidazol-2-ylmethyl)-L-ornithyl-L-aspartyl-D-alanyl-L-aspartyl-glycyl-D-seryl-*threo*-3-methyl-L-glutamyl-3-anthraniloyl-L-alanine *C*-1.13-*O*-2.4-lactone



C76 H105 N19 O26; Mol wt: 1700.7720

ACTION – Antibacterial agent, an ornithine heterocyclic analogue of daptomycin with strong activity against Gram-positive bacteria including methicillin-sensitive and -resistant *Staphylococcus aureus* (MIC = 0.78 and 0.39 μg/ml, respectively), *Enterococcus faecium* and *Enterococcus faecalis* (MIC = 1.56 μg/ml). *In vivo*, compound exhibited comparable efficacy to daptomycin in protecting mice against septicemia caused by methicillin-resistant *S. aureus* (PD₅₀ = 0.22 mg/kg i.p.). Other related compounds are:



Compound	R1	Formula
325712	1-Me-2-imidazolyl	C ₇₇ H ₁₀₇ N ₁₉ O ₂₆
325713	4-Cl-2-quinolinyl	C ₈₂ H ₁₀₇ ClN ₁₈ O ₂₆
325714	6-N(Me)2-2-quinolinyl	C ₈₄ H ₁₁₃ N ₁₉ O ₂₆

SOURCE – Cubist Pharmaceuticals.

REFERENCES

1. Hill, J. et al. (Cubist Pharmaceuticals, Inc.) *Lipopeptides as antibacterial agents.* WO 0144274.

2. Yu, X.Y. et al. *Synthesis and biological activity of ornithine heterocyclic analogs of daptomycin.* 42nd Intersci Conf Antimicrob Agents Chemother (Sept 27-30, San Diego) 2002, Abst F-349.

5. *Vertex continues to advance broad clinical pipeline.* DailyDrugNews.com (Daily Essentials) 2001, Aug 2.
6. *Vertex expands product pipeline.* DailyDrugNews.com (Daily Essentials) 2000, Oct 30.
7. *Vertex offers progress report for first half of 2002.* DailyDrugNews.com (Daily Essentials) 2002, July 24.
8. *Vertex reports Q1 2001 results.* DailyDrugNews.com (Daily Essentials) 2001, April 30.
9. *Vertex updates its progress and plans for 2002.* DailyDrugNews.com (Daily Essentials) 2002, Jan 15.
10. *Vertex updates latest R&D progress.* DailyDrugNews.com (Daily Essentials) 2002, Nov 22.
11. *VX-148 enters clinical development.* DailyDrugNews.com (Daily Essentials) 2000, Dec 22.

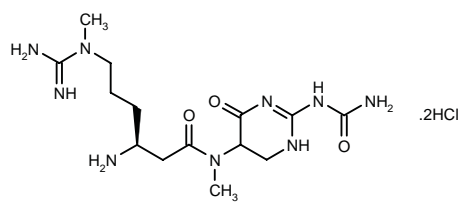
*Identified compound **295178** (see **295175**) Drug Data Rep 2001, 023(02): 0173.

ANTIINFECTIVE THERAPY

ANTIBIOTICS

324612

3(S)-Amino-*N*-methyl-6-(1-methylguanidino)-*N*-(4-oxo-2-ureido-1,4,5,6-tetrahydropyrimidin-5-yl)hexanamide dihydrochloride



C14 H27 N9 O3 . 2HCl; Mol wt: 442.3491

ACTION – Antibiotic derived from the natural compound TAN-1057 that acts by inhibiting bacterial translation (IC₅₀ = 0.06 μM) and is active against Gram-positive pathogens including *Staphylococcus aureus*, *Staphylococcus epidermidis* and *Streptococcus pyogenes* (MIC = 0.025, 0.12 and 0.5 μg/ml, respectively). *In vivo*, compound protected mice from systemic infections produced by *S. aureus* with an ED₁₀₀ < 0.5 mg/kg i.v.

SOURCE – Bayer.

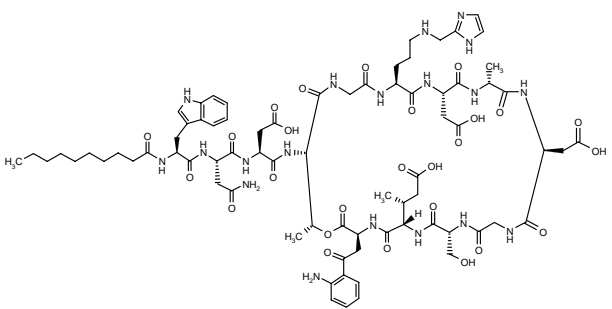
REFERENCES

1. Brands, M. et al. (Bayer AG) *TAN-1057 derivs.* DE 19838998, EP 1117652, JP 2002523496, WO 0012484.

2. Brands, M. et al. *Novel antibiotics for the treatment of Gram-positive bacterial infections.* J Med Chem 2002, 45(19): 4246.

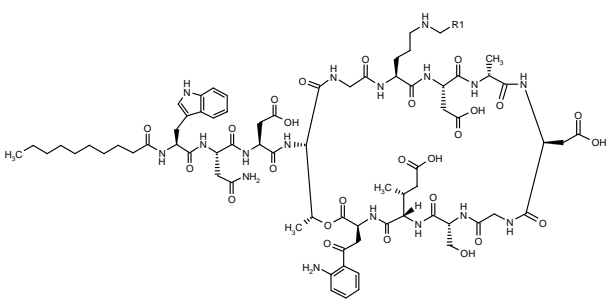
325711

N-Decanoyl-L-tryptophyl-L-asparaginyl-L-aspartyl-L-threonyl-glycyl-*N*⁵-(1*H*-imidazol-2-ylmethyl)-L-ornithyl-L-aspartyl-D-alanyl-L-aspartyl-glycyl-D-seryl-*threo*-3-methyl-L-glutamyl-3-anthraniloyl-L-alanine C-1.13-*O*-2.4-lactone



C76 H105 N19 O26; Mol wt: 1700.7720

ACTION – Antibacterial agent, an ornithine heterocyclic analogue of daptomycin with strong activity against Gram-positive bacteria including methicillin-sensitive and -resistant *Staphylococcus aureus* (MIC = 0.78 and 0.39 μg/ml, respectively), *Enterococcus faecium* and *Enterococcus faecalis* (MIC = 1.56 μg/ml). *In vivo*, compound exhibited comparable efficacy to daptomycin in protecting mice against septicemia caused by methicillin-resistant *S. aureus* (PD₅₀ = 0.22 mg/kg i.p.). Other related compounds are:



Compound	R1	Formula
325712	1-Me-2-imidazolyl	C ₇₇ H ₁₀₇ N ₁₉ O ₂₆
325713	4-Cl-2-quinolinyl	C ₈₂ H ₁₀₇ ClN ₁₈ O ₂₆
325714	6-N(Me)2-2-quinolinyl	C ₈₄ H ₁₁₃ N ₁₉ O ₂₆

SOURCE – Cubist Pharmaceuticals.

REFERENCES

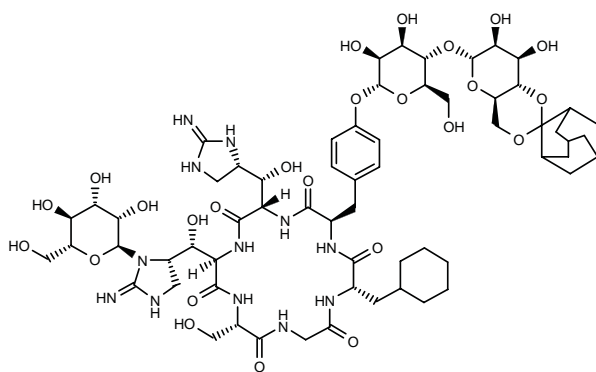
1. Hill, J. et al. (Cubist Pharmaceuticals, Inc.) *Lipopeptides as antibacterial agents.* WO 0144274.

2. Yu, X.Y. et al. *Synthesis and biological activity of ornithine heterocyclic analogs of daptomycin.* 42nd Intersci Conf Antimicrob Agents Chemother (Sept 27-30, San Diego) 2002, Abst F-349.

AC98-6446

325498

(3*S*,6*R*,9*S*,12*R*,15*S*)-12-[4-[4-[4,6-*O*-(2-Adamantylidene)- α -D-mannopyranosyloxy]- α -D-mannopyranosyloxy]-benzyl]-15-cyclohexylmethyl-9-[1(*S*)-hydroxy-1-[2-iminoimidazolidin-4(*S*)-yl]methyl]-6-[1(*R*)-hydroxy-1-[2-imino-3-(α -D-mannopyranosyl)imidazolidin-4(*S*)-yl]methyl]-3-(hydroxymethyl)-1,4,7,10,13,16-hexaazacyclo-octadecane-2,5,8,11,14,17-hexaone



C63 H94 N12 O25; Mol wt: 1419.4950

ACTION – Semisynthetic mannopeptimycin derivative with excellent antibacterial activity against Gram-positive microorganisms including methicillin-susceptible and -resistant *Staphylococcus aureus* (MIC₉₀ = 0.06 and 0.03 µg/ml, respectively), vancomycin-susceptible and -resistant *Enterococcus faecalis* (MIC₉₀ = 0.25 and 0.12 µg/ml, respectively) and *Enterococcus faecium* (MIC₉₀ = 0.25 and 0.12 µg/ml, respectively), as well as penicillin-susceptible, -intermediate and -resistant *Streptococcus pneumoniae* (MIC₉₀ < 0.008-0.03 µg/ml). Furthermore, it was effective against coagulase-negative staphylococci (MIC₉₀ = 0.03 µg/ml). Compound showed bactericidal activity against most staphylococcal and streptococcal isolates including methicillin-resistant *S. aureus* and penicillin-resistant *S. pneumoniae*; a significant postantibiotic effect of 2.4- > 4.0 h was seen against staphylococci and enterococci. *In vivo*, it was significantly more effective than vancomycin against lethal infections caused by methicillin-susceptible or -resistant *S. aureus*, vancomycin-resistant *E. faecalis* and penicillin-susceptible or -resistant *S. pneumoniae* (ED₅₀ = 0.05-0.39 mg/kg i.v.). It was also effective in protecting mice against high infections caused by *S. aureus* (1 mg/kg i.v. and 10 mg/kg s.c.) and produced a significant reduction in bacterial titers in endocarditis models at doses of 1-10 mg/kg i.v.

SOURCE – Wyeth.

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2. Dushin, R.G. et al. *Synthesis of AC98-6446, a semisynthetic mannopeptimycin derivative*. 42nd Intersci Conf Antimicrob Agents Chemother (Sept 27-30, San Diego) 2002, Abst F-352.
3. Labthalvikul, P. et al. *Effect of inoculum, pH and biofilm on the in vitro activity of AC98-6446 the novel semi-synthetic cyclic glycopeptide of AC98*. 42nd Intersci Conf Antimicrob Agents Chemother (Sept 27-30, San Diego) 2002, Abst F-355.
4. Murphy, T.M. et al. *In vivo efficacy and pharmacokinetics of AC98-6446, a novel cyclic glycopeptide, in experimental models of infection*. 42nd Intersci Conf Antimicrob Agents Chemother (Sept 27-30, San Diego) 2002, Abst F-356.

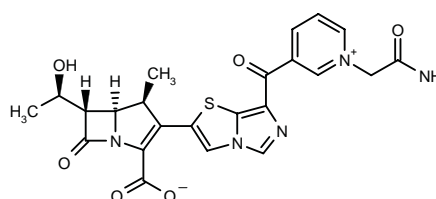
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6. Petersen, P.J. et al. *Time kill kinetics and postantibiotic effects (PAE) of the AC98 novel semisynthetic cyclic glycopeptide antibiotic derivative AC98-6446*. 42nd Intersci Conf Antimicrob Agents Chemother (Sept 27-30, San Diego) 2002, Abst F-354.

CP-5609*

322446

(1*R*,5*S*,6*S*)-2-[7-[1-(Carbamoylmethyl)pyridin-1-ium-3-ylcarbonyl]imidazo[5,1-*b*]thiazol-2-yl]-6-[1(*R*)-hydroxyethyl]-1-methyl-1-carba-2-penem-3-carboxylate



C23 H21 N5 O6 S; Mol wt: 495.5139

ACTION – Carbapenem antibiotic with strong antibacterial activity against Gram-positive and Gram-negative bacteria including clinical isolates of methicillin-resistant *Staphylococcus aureus* (MRSA; MIC₉₀ = 2 µg/ml), penicillin-resistant *Streptococcus pneumoniae* (PRSP; MIC₉₀ = 0.031 µg/ml) and β -lactamase-negative ampicillin-resistant *Haemophilus influenzae* (BLNAR; MIC₉₀ = 0.25 µg/ml); it was more potent than vancomycin, meropenem, imipenem, cefotaxime and flomoxef against these strains. Its strong activity against MRSA may be attributable to its high affinity for the penicillin-binding protein PBP2a (IC₅₀ = 0.73 µg/ml). *In vivo*, compound was more effective than reference compounds against respiratory tract infections in mice caused by MRSA, PRSP and BLNAR and meningitis caused by PRSP; it was also active in a model of experimental endocarditis caused by MRSA in rats, where it was found to be more effective than vancomycin against both progressive and established infections. Preclinical toxicological evaluation in rats, mice and rabbits indicated the safety of compound for clinical use in humans

SOURCE – Meiji Seika.

REFERENCES

1. Kano, Y. et al. (Meiji Seika Kaisha, Ltd.) *Novel carbapenem derivs*. WO 0242312.
2. Kurazono, M. et al. *CP5609, a novel parenteral carbapenem: In vitro activities against methicillin-resistant S. aureus, penicillin-resistant S. pneumoniae and beta-lactamase negative ampicillin-resistant H. influenzae*. 42nd Intersci Conf Antimicrob Agents Chemother (Sept 27-30, San Diego) 2002, Abst F-320.
3. Matsuhisa, E. et al. *CP5609, a novel parenteral carbapenem: Pre-clinical toxicological profile*. 42nd Intersci Conf Antimicrob Agents Chemother (Sept 27-30, San Diego) 2002, Abst F-323.
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5. Shitara, E. et al. *CP5609, a novel parenteral carbapenem: Synthesis and structure-activity relationships*. 42nd Intersci Conf Antimicrob Agents Chemother (Sept 27-30, San Diego) 2002, Abst F-319.

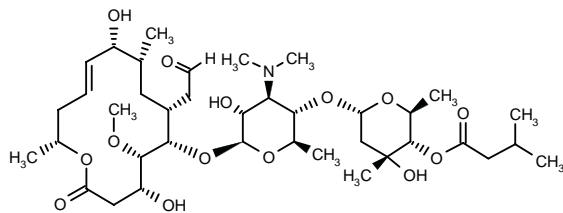
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*Identified compound **322446** Drug Data Report 2002, 024(09): 0813.

EP-1052

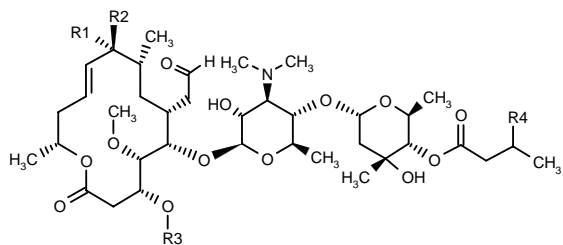
325548

[(4*R*,5*S*,6*S*,7*R*,9*R*,10*R*,14*R*)-6-[3,6-Dideoxy-4-*O*-[2,6-dideoxy-3-*C*-methyl-4-*O*-(3-methylbutyryl)- α -L-ribo-hexopyranosyl]-3-(dimethylamino)- β -D-glucopyranosyl]-4,10-dihydroxy-5-methoxy-9,14-dimethyl-2-oxooxacyclo-tetradec-11-en-7-yl]acetaldehyde



C38 H65 N O14; Mol wt: 759.9245

ACTION – Macrolide antibiotic with MIC values of 2 μ g/ml against erythromycin-susceptible *Staphylococcus aureus* and 0.25 μ g/ml against erythromycin-susceptible *Streptococcus pneumoniae*. Compared to erythromycin, it exhibited improved antibacterial activity against erythromycin-resistant *S. pneumoniae* and *Streptococcus pyogenes* (MIC = 0.125-0.25 vs. 8-16 μ g/ml). Other related compounds are:



Compound	R1	R2	R3	R4	Formula
EP-263 [325481]	OH	H	Ac	Me	C ₄₀ H ₆₇ NO ₁₅
EP-1126 [325546]	OH	H	H	H	C ₃₇ H ₆₃ NO ₁₄
EP-343 [325547]	-O-		Ac	Me	C ₄₀ H ₆₅ NO ₁₅

SOURCE – Enanta Pharmaceuticals.

REFERENCES

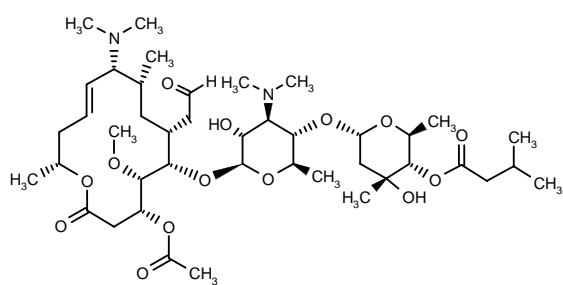
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2. Lazarova, T.I. et al. *Synthesis and biological evaluation of a new class of 14-membered ring macrolide antibiotics*. 42nd Intersci Conf Antimicrob Agents Chemother (Sept 27-30, San Diego) 2002, Abst F-1665.

EP-1112

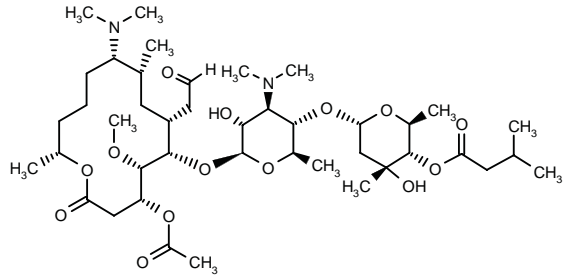
325540

Acetic acid (4*R*,5*S*,6*S*,7*R*,9*R*,10*R*,14*R*)-6-[3,6-dideoxy-4-*O*-[2,6-dideoxy-3-*C*-methyl-4-*O*-(3-methylbutyryl)- α -L-ribo-hexopyranosyl]-3-(dimethylamino)- β -D-glucopyranosyl]-10-(dimethylamino)-5-methoxy-9,14-dimethyl-2-oxo-7-(2-oxoethyl)oxacyclotetradec-11-en-4-yl ester



C42 H72 N2 O14; Mol wt: 829.0308

ACTION – Macrolide antibiotic active against erythromycin-susceptible strains of *Staphylococcus aureus* (MIC = 2 μ g/ml) and *Streptococcus pneumoniae* (MIC = 0.06 μ g/ml), as well as erythromycin-resistant strains of *S. pneumoniae* (MIC = 0.06 μ g/ml) and *Streptococcus pyogenes* (MIC = 0.125 μ g/ml). Another related compound is:



EP-935 [325535]: C42 H74 N2 O14

SOURCE – Enanta Pharmaceuticals.

REFERENCES

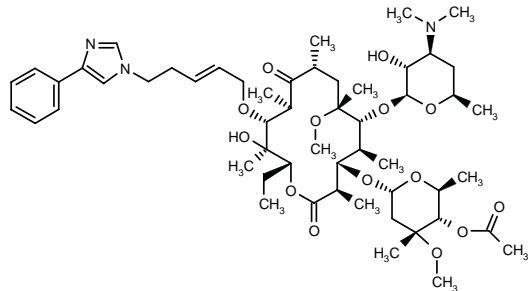
1. Or, Y.S. et al. (Enanta Pharmaceuticals, Inc.) *9-Amino-14-membered macrolides derived from leucomycins*. US 6436906.

2. Vo, N.H. et al. *9-Amino derivatives of novel 14-membered ring macrolide antibiotics derived from leucomycins: Chemistry and in vitro biological activities*. 42nd Intersci Conf Antimicrob Agents Chemother (Sept 27-30, San Diego) 2002, Abst F-1664.

EP-1579

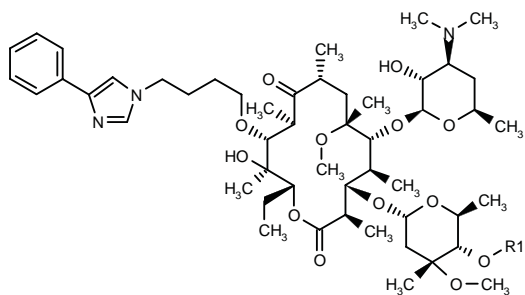
325544

4''-Acetyl-6-*O*-methyl-11-*O*-[5-(4-phenyl-1*H*-imidazol-1-yl)-2-pentenyl]erythromycin A

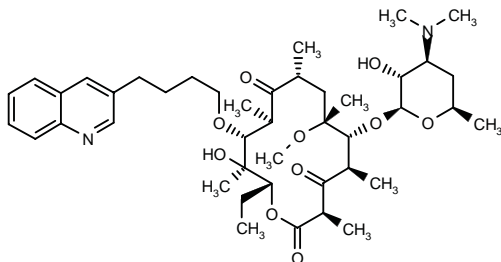


C54 H85 N3 O14; Mol wt: 1000.2730

ACTION – Macrolide antibiotic, an analogue of erythromycin with improved antibacterial activity against erythromycin-resistant strains of *Streptococcus pneumoniae* and *Streptococcus pyogenes* (MIC = 0.13-4 µM) and comparable activity against erythromycin-susceptible strains of *Staphylococcus aureus* and *Streptococcus pneumoniae* (MIC = 2 and 0.06 µg/ml, respectively). Other related compounds are:



Compound	R1	Formula
EP-1549 [325541]	Ac	C ₅₃ H ₈₅ N ₃ O ₁₄
EP-1553 [325543]	H	C ₅₁ H ₈₃ N ₃ O ₁₃



EP-1567 [325545]: C43 H66 N2 O10

SOURCE – Enanta Pharmaceuticals.

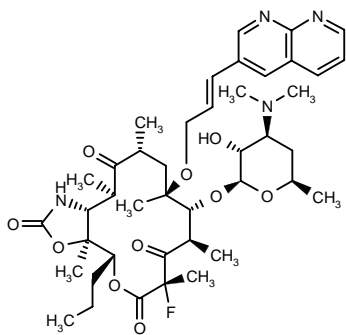
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JNJ-17155437

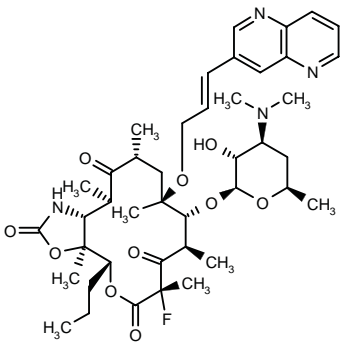
325563

11-Amino-11-deoxy-3-des(hexopyranosyloxy)-2-fluoro-15-methyl-3-oxo-6-O-[3-(1,8-naphthyridin-3-yl)-2-propenyl]erythromycin A 11-N,12-O-cyclic carbamate



C42 H59 F N4 O10; Mol wt: 798.9441

ACTION – Ketolide antibiotic with comparable activity to telithromycin against a panel of respiratory pathogens including macrolide-susceptible and -resistant pneumococci (MIC = 0.015-0.12 µg/ml) and *Haemophilus influenzae* (MIC = 1-2 µg/ml). Like telithromycin, compound inhibited protein synthesis (IC₅₀ = 0.27 and 0.24 µM, respectively) and was bacteriostatic against both macrolide-susceptible and -resistant *S. pneumoniae* strains. Another related compound is:



JNJ-17155528 [325564]: C42 H59 F N4 O10

SOURCES – Johnson & Johnson; Kosan.

REFERENCES

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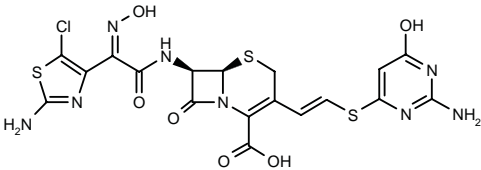
2. Abbanat, D. et al. *In vitro antibacterial activities of naphthyridine-containing ketolides*. 42nd Intersci Conf Antimicrob Agents Chemother (Sept 27-30, San Diego) 2002, Abst F-1663.

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LB-11058

325263

(6*R*,7*R*)-7-[(*Z*)-2-(2-Amino-5-chlorothiazol-4-yl)-2-(hydroxyimino)acetamido]-3-[(*E*)-2-(2-amino-6-hydroxypyrimidin-4-ylsulfanyl)vinyl]-3-cephem-4-carboxylic acid



C18 H15 Cl N8 O6 S3; Mol wt: 571.0175

ACTION – Parenteral cephalosporin antibiotic with potent antibacterial activity against multidrug-resistant Gram-positive bacteria including methicillin-resistant *Staphylococcus aureus* (MRSA; MIC₉₀ = 2 µg/ml), methicillin-resistant *Staphylococcus epidermidis* (MRSE; MIC₉₀ = 1 µg/ml) and vancomycin-resistant *Enterococcus faecalis* (VRE; MIC₉₀ = 4 µg/ml), as well as certain respiratory tract pathogens including penicillin-resistant *Streptococcus pneumoniae* (MIC₉₀ = 0.25 µg/ml), *Haemophilus influenzae* (MIC₉₀ = 0.25 µg/ml) and *Moraxella catarrhalis* (MIC₉₀ = 0.25 µg/ml). It was also active against vancomycin-resistant Gram-negative microorganisms including *Escherichia coli* (MIC = 1 µg/ml), *Salmonella typhimurium* (MIC = 2 µg/ml) and *Proteus vulgaris* (MIC = 0.5 µg/ml). Compound was more active than vancomycin,

linezolid and Synercid® (quinupristin/dalfopristin) against Gram-positive bacteria, it killed bacteria more rapidly than vancomycin and exhibited good affinity for staphylococcal penicillin-binding proteins ($IC_{50} = 0.3 \mu\text{g/ml}$ for PBP-2a). *In vivo*, it demonstrated excellent activity in mouse systemic infections produced by MRSA and VRE ($ED_{50} = 7.5$ and 25 mg/kg i.v.), as well as in rats with pneumococcal pneumonia caused by both penicillin-susceptible and -resistant strains. No acute toxicity was seen in mice following i.v. administration of 500 mg/kg .

SOURCE – LG Chem Investment.

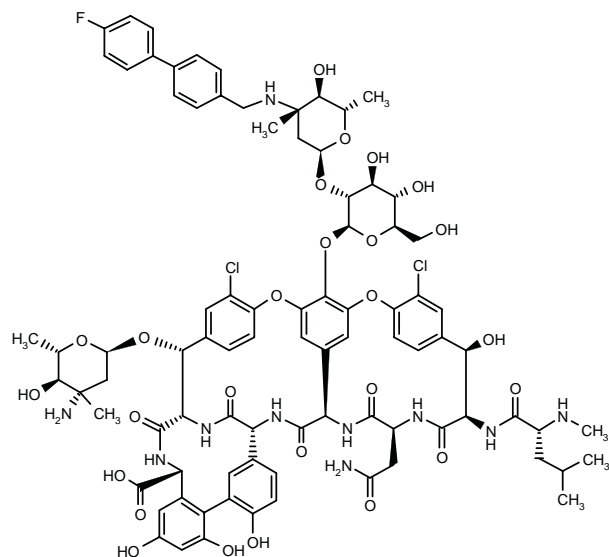
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2. Joo, H.Y. et al. *The in vivo efficacy & pharmacokinetic profile of LB11058, a new parenteral cephalosporin in experimental animals*. 42nd Intersci Conf Antimicrob Agents Chemother (Sept 27-30, San Diego) 2002, Abst F-331.
3. Lee, C. et al. *Synthesis and antibacterial activities of LB11058, a novel anti-MRSA cephalosporin antibiotic*. 42nd Intersci Conf Antimicrob Agents Chemother (Sept 27-30, San Diego) 2002, Abst F-329.

LY-329332

325504

(3*S*,6*R*,7*R*,22*R*,23*S*,26*S*,36*R*,38*aR*)-22-(3-Amino-2,3,6-trideoxy-3-*C*-methyl- α -L-mannopyranosyloxy)-3-(carbamoylmethyl)-10,19-dichloro-44-[2-*O*-[3-(4'-fluorobiphenyl-4-ylmethylamino)-2,3,6-trideoxy-3-*C*-methyl- α -L-mannopyranosyl]- β -D-glucopyranosyloxy]-7,28,30,32-tetrahydroxy-6-(*N*²-methyl-D-leucylamido)-2,5,24,38,39-pentaoxo-2,3,4,5,6,7,23,24,25,26,36,37,38,38*a*-tetradecahydro-1*H*,22*H*-8,11:18,21-dietheno-23,26-(imino-methano)-13,16:31,35-dimetheno[1,6,9]oxadiazacyclohexadecino[4,5-*m*][10,2,16]benzoxadiazacyclopentacosine-26-carboxylic acid



C86 H97 Cl2 F N10 O26; Mol wt: 1776.6600

ACTION – Glycopeptide antibiotic with improved potency compared to vancomycin against vancomycin-sensitive and -resistant strains of *Enterococcus faecium* (MIC = 0.03 and $0.5 \mu\text{g/ml}$, respectively, vs. 2 and $512 \mu\text{g/ml}$, respectively, for vancomycin). Studies to elucidate the mechanism of action of compound showed that it, like vancomycin, inhibits transglycosylase activity.

SOURCE – Lilly.

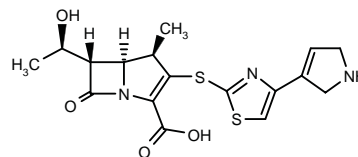
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4. Kim, S.J. et al. *REDOR characterization of vancomycin binding sites in S. aureus*. Biophys J 2002, 82(1, Part 2): Abst.
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6. Rodriguez, M.J. et al. *Novel glycopeptide antibiotics: N-Alkylated derivatives active against vancomycin-resistant enterococci*. J Antibiot 1998, 51(6): 560.

SM-197436

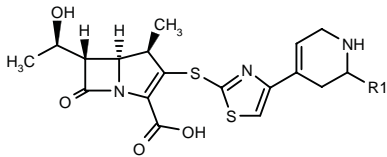
313172

(1*R*,5*S*,6*S*)-2-[4-(2,5-Dihydro-1*H*-pyrrol-3-yl)thiazol-2-ylsulfanyl]-6-[1(*R*)-hydroxyethyl]-1-methyl-1-carba-2-penem-3-carboxylic acid



C17 H19 N3 O4 S2; Mol wt: 393.4861

ACTION – Carbapenem antibiotic with strong antibacterial activity against Gram-positive cocci including methicillin-resistant *Staphylococcus aureus* and *Staphylococcus epidermidis* (MIC = $2 \mu\text{g/ml}$), penicillin-resistant *Streptococcus pneumoniae* (MIC = $0.25 \mu\text{g/ml}$), and ampicillin- and vancomycin-resistant *Enterococcus faecium* (MIC = $4 \mu\text{g/ml}$). It was also active against Gram-negative bacteria including *Escherichia coli*, *Klebsiella pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis* and *Neisseria* spp. (MIC < 0.008 - $0.5 \mu\text{g/ml}$). Compound exhibited comparable or higher stability toward human renal dehydropeptidase I (DHP-I) and slightly higher binding affinity for human plasma proteins compared to imipenem. No systemic toxicity was seen in mice up to 500 mg/kg i.v. Other related compounds are:



Compound	R1	Formula
SM-232721 [313173]	(R)-CH2OH	C ₁₉ H ₂₃ N ₃ O ₅ S ₂
SM-232724 [313174]	(R)-Me	C ₁₉ H ₂₃ N ₃ O ₄ S ₂

SOURCES – Roche; Sumitomo Pharmaceuticals.

REFERENCES

1. Sunagawa, M. et al. (Sumitomo Pharmaceuticals Co., Ltd.) *Novel β-lactam cpds. and process for producing the same*. WO 0238564.

2. Sunagawa, M. et al. *New anti-MRSA and anti-VRE carbapenems; synthesis and structure-activity relationships of 1β-methyl-2-(thiazol-2-ylthio)carbapenems*. J Antibiot 2002, 55(8): 722.

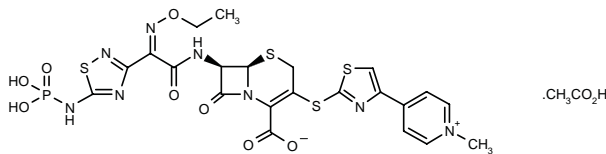
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4. Ueda, Y. and Sunagawa, M. *New parenteral 2-(thiazol-2-ylthio)-1β-methylcarbapenems; Antimicrobial spectrum including drug-resistant Gram-positive bacteria*. 41st Intersci Conf Antimicrob Agents Chemother (Dec 16-19, Chicago) 2001, Abst F-364.

TAK-599^{1,3,4}

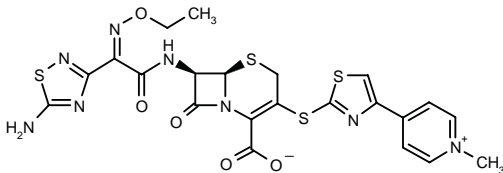
325265

(6*R*,7*R*)-7-[(*Z*)-2-(Ethoxyimino)-2-[5-(phosphonoamino)-1,2,4-thiadiazol-3-yl]acetamido]-3-[4-(1-methylpyridinium-4-yl)thiazol-2-ylsulfany]-3-cephem-4-carboxylate acetate



C22 H21 N8 O8 P S4 . C2 H4 O2; Mol wt: 744.7455

ACTION – Parenteral cephalosporin antibiotic, a water-soluble prodrug of **T-91825**, a potent antibacterial agent with comparable activity to vancomycin, teicoplanin and linezolid against methicillin-resistant *Staphylococcus aureus* (MRSA; MIC = 1 µg/ml). The prodrug showed excellent water solubility (> 100 mg/ml at pH of 7.0), good stability in the solid state and solution, and was rapidly converted to the parent antibiotic in blood following i.v. administration to rats and monkeys. The prodrug was effective against local and systemic infections in mice caused by MRSA, with activity superior to vancomycin and linezolid.



T-91825 [325264]^{2,3,4}: C22 H20 N8 O5 S4

SOURCE – Takeda.

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2. Tawada, H. and Koshiki, K. (Takeda Chemical Industries, Ltd.) *Cephem cpds., method for their preparation and antibacterial compsns*. JP 1997100283.

3. Iizawa, Y. et al. *TAK-599, a novel N-phosphono type prodrug of anti-MRSA cephalosporin T-91825: In vitro and in vivo antibacterial activity*. 42nd Intersci Conf Antimicrob Agents Chemother (Sept 27-30, San Diego) 2002, Abst F-333.

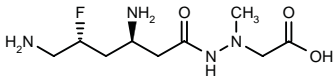
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VRC-4219

313026

2-[2-[3(*S*),6-Diamino-5(*R*)-fluorohexanoyl]-1-methylhydrazino]acetic acid

3(*S*),6-Diamino-5(*R*)-fluorohexanoic acid 2-(carboxymethyl)-2-methylhydrazide



C9 H19 F N4 O3; Mol wt: 250.2721

ACTION – Bactericidal protein synthesis inhibitor (IC₅₀ = 1.8 µM) belonging to the negamycin class of antibiotics with strong activity against *Escherichia coli*, *Klebsiella pneumoniae* and *Enterobacter cloacae* (MIC = 2-8 µg/ml), but lower activity against *Pseudomonas aeruginosa*, *Haemophilus influenzae*, *Staphylococcus aureus* and *Streptococcus pneumoniae* (MIC = 32 µg/ml). It showed bactericidal activity against *E. coli*, *S. aureus* and *P. aeruginosa*, and a long postantibiotic effect against *S. aureus* (> 3.5 h) and *E. coli* (4.8 h). *In vivo*, it exhibited strong efficacy in several murine models of septicemia induced by *E. coli* (ED₅₀ = 4.1 and 15.1 mg/kg i.v. and p.o., respectively), *K. pneumoniae*, *P. aeruginosa* and *S. aureus* (ED₅₀ = 7.1, 40.2 and 32.4 mg/kg i.v., respectively). Compound showed a good pharmacokinetic profile with an oral bioavailability in mice of 16%; it was rapidly excreted into urine. Low systemic toxicity was seen in mice following a single i.v. dose; the maximum tolerated dose (MTD) was > 500 mg/kg.

SOURCE – Versicor.

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2. Hackbarth, C.J. et al. *VRC4219, a novel bactericidal antibiotic with in vivo efficacy*. 41st Intersci Conf Antimicrob Agents Chemother (Dec 16-19, Chicago) 2001, Abst F-1708.

3. Rafanan, N. et al. *Resistance to VRC4219 in E. coli*. 42nd Intersci Conf Antimicrob Agents Chemother (Sept 27-30, San Diego) 2002, Abst F-1682.

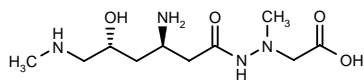
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VRC-4334

325662

3(*R*)-Amino-5(*R*)-hydroxy-6-(methylamino)hexanoic acid 2-(carboxymethyl)-2-methylhydrazide

2-[2-[3(*R*)-Amino-5(*R*)-hydroxy-6-(methylamino)-hexanoyl]-1-methylhydrazino]acetic acid



C10 H22 N4 O4; Mol wt: 262.3078

ACTION – Bactericidal protein synthesis inhibitor (IC₅₀ = 2.3 μM), a derivative of the naturally produced negamycin with *in vitro* antibacterial activity against *Escherichia coli*, *Klebsiella pneumoniae* and *Enterobacter cloacae* (MIC = 4-16 μg/ml). It was effective *in vivo* in an *E. coli* septicemia infection model in mice (ED₅₀ = 16.5 mg/kg i.v. vs. 2.3 mg/kg i.v. for ampicillin).

SOURCE – Versicor.

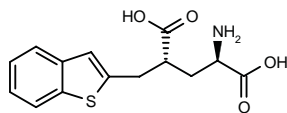
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ANTIBACTERIAL DRUGS

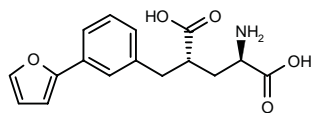
325325

4(*R*)-(1-Benzothien-2-ylmethyl)-D-glutamic acid



C14 H15 N O4 S; Mol wt: 293.3415

ACTION – Antibacterial agent, an inhibitor of glutamate racemase (Murl; IC₅₀ = 0.036 μg/ml) with selective antibacterial activity against *Streptococcus pneumoniae* (MIC = 0.24 μg/ml for both). *In vivo*, the dose of 40 mg/kg i.p. completely suppressed bacterial growth in mice with thigh infection caused by *S. pneumoniae*. Another related compound is:



325329: C16 H17 N O5

SOURCE – Lilly.

REFERENCES

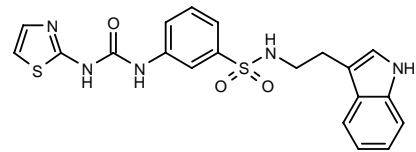
1. De Dios, A. et al. (Eli Lilly and Company) *Chemical cpds*. WO 0214261.

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325568

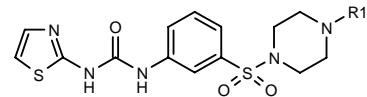
N-[2-(1*H*-Indol-3-yl)ethyl]-3-[3-(2-thiazolyl)ureido]-benzenesulfonamide

N-[3-[*N*-2-(1*H*-Indol-3-yl)ethyl]sulfamoyl]phenyl]-*N*'-(2-thiazolyl)urea



C20 H19 N5 O3 S2; Mol wt: 441.5341

ACTION – Antibacterial agent, a potent, selective and competitive inhibitor of Gram-positive and Gram-negative phenylalanine-tRNA ligase (IC₅₀ = 8, 8, 50 and 200 nM against *Escherichia coli*, *Haemophilus influenzae*, *Staphylococcus aureus* and *Streptococcus pneumoniae* enzyme, respectively) with strong selectivity over mammalian enzyme (IC₅₀ > 200 μM against rabbit and human enzyme). Compound displayed good antibacterial activity against *S. aureus*, *S. pneumoniae*, *H. influenzae* and *Branhamella catarrhalis* (MIC = 1.5, 12, 0.4 and 1.5 μg/ml, respectively); this activity was partly antagonized by increasing concentrations of phenylalanine in the culture broth. In systemic infections induced by *S. aureus* in mice and *S. pneumoniae* in rats, a dose of 100 mg reduced bacterial load by up to 3 orders of magnitude. Other related compounds are:



Compound	R1	Formula
325571	cyclopentyl-CO	C ₂₀ H ₂₅ N ₅ O ₄ S ₂
325706	3-OH-Ph	C ₂₀ H ₂₁ N ₅ O ₄ S ₂

SOURCE – Bayer.

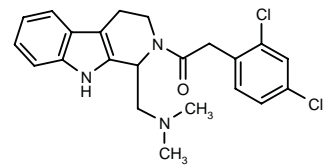
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2. Brötz, H. et al. *In vitro and in vivo antimicrobial activity of novel phenylalanine-tRNA synthetase inhibitors*. 42nd Intersci Conf Antimicrob Agents Chemother (Sept 27-30, San Diego) 2002, Abst F-757.

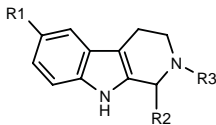
325585

2-(2,4-Dichlorophenyl)-1-[1-(dimethylaminomethyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-2-yl]ethanone



C22 H23 Cl2 N3 O; Mol wt: 416.3497

ACTION – β -Carboline derivative for use in the treatment of bacterial infections. Other specifically claimed compounds include the following:



Compound	R1	R2	R3	Formula
325586	Cl	CH2N(Me)2	3,4-(Cl)2-PhCO	C ₂₁ H ₂₀ Cl ₃ N ₃ O
325587	Me	CH2N(Me)2	3,4-(Cl)2-PhCO	C ₂₂ H ₂₃ Cl ₂ N ₃ O
325588	H	4-F-Ph	4-OH-PhCO	C ₂₄ H ₁₉ FN ₂ O ₂
325589	H	4-F-Ph	3-Cl-4-OH-PhCO	C ₂₄ H ₁₈ ClFN ₂ O ₂
325590	H	4-OH-PhCO	4-(CO2Me)-Ph	C ₂₆ H ₂₂ N ₂ O ₄
325591	H	4-OH-Ph	3-Me-4-OH-PhCO	C ₂₅ H ₂₂ N ₂ O ₃
325593	H	4-OH-Ph	4-OH-PhCO	C ₂₄ H ₂₀ N ₂ O ₃

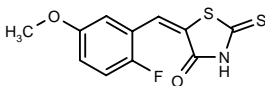
SOURCE – GlaxoSmithKline.

REFERENCES

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325792

5-(2-Fluoro-5-methoxybenzylidene)-2-thioxothiazolidin-4-one



C11 H8 F N O2 S2; Mol wt: 269.3192

ACTION – A representative compound from a series of thiazolidinediones with antibacterial activity, demonstrating *in vitro* activity against *Staphylococcus aureus* Oxford (MIC = 4 μ g/ml), *S. aureus* WCUH29 (MIC = 2 μ g/ml), *Haemophilus influenzae* Q1 (MIC = 4 μ g/ml), *H. influenzae* NMEC1 (MIC = 16 μ g/ml), *Moraxella catarrhalis* 1502 (MIC = 4 μ g/ml) and *Streptococcus pneumoniae* ERY2 (MIC = 64 μ g/ml). Potentially useful for the treatment of respiratory tract, urinary tract, soft tissue, bone and joint, and systemic infections, and also meningitis, endocarditis and sexually transmitted diseases.

SOURCE – GlaxoSmithKline.

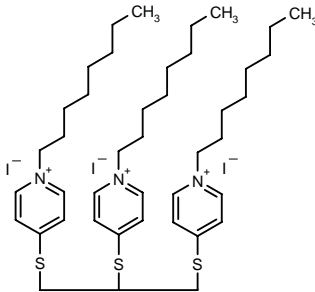
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326076

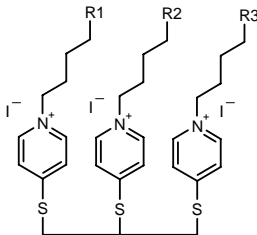
4,4',4''-(Propane-1,2,3-triyl)tris(sulfanyl)tris(1-octylpyridinium iodide)

4TP-8



C42 H68 I3 N3 S3; Mol wt: 1091.9180

ACTION – Antibacterial agent with *in vitro* activity against a panel of bacterial strains including *Escherichia coli*, *Bacillus subtilis*, *Klebsiella pneumoniae*, *Staphylococcus aureus* and *Proteus rettgeri*, with MBCs < 2 μ g/ml. This compound displayed hemolytic activity against human erythrocytes at > 50 μ g/ml. Other exemplified tris(pyridinium) derivatives are:



Compound	R1	R2	R3	Formula
326077	H	H	H	C ₃₀ H ₄₄ I ₃ N ₃ S ₃
326078	Et	Et	Et	C ₃₆ H ₅₆ I ₃ N ₃ S ₃

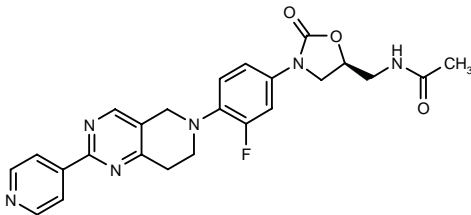
SOURCE – Toagosei.

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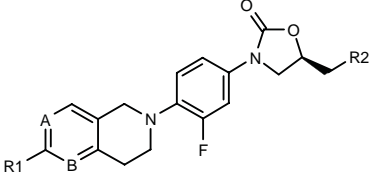
326237

N-[3-[3-Fluoro-4-[2-(4-pyridyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-6-yl]phenyl]-2-oxooxazolidin-5(S)-ylmethyl]acetamide

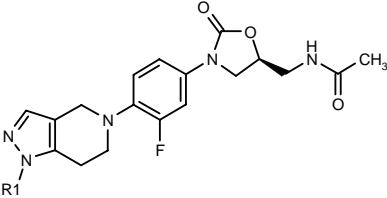


C24 H23 F N6 O3; Mol wt: 462.4827

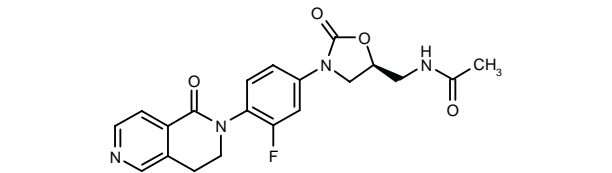
ACTION – Antibacterial oxazolidinone that gave MIC values of 2, 2 and 4 µg/ml, respectively, against *Staphylococcus aureus* OC4172, *S. aureus* OC2878 and *Enterococcus faecium* OC3312 in *in vitro* testing. Potentially useful for the treatment of infections caused by *S. aureus*, *Staphylococcus epidermidis*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Enterococcus* spp., *Moraxella catarrhalis* and *Haemophilus influenzae*. Other exemplified compounds are:



Compound	R1	R2	A	B	Formula
326238	H	OH	CH	CH	C ₁₉ H ₁₉ FN ₂ O ₃
326239	H	NHAc	CH	CH	C ₂₁ H ₂₂ FN ₃ O ₃
326240	H	NHAc	N	CH	C ₂₀ H ₂₁ FN ₄ O ₃
326242	H	NHAc	N	N	C ₁₉ H ₂₀ FN ₅ O ₃
326243	Me	NHAc	N	N	C ₂₀ H ₂₂ FN ₅ O ₃
326244	2-Me-4-thiazolyl	NHAc	N	N	C ₂₃ H ₂₃ FN ₆ O ₃ S
326245	2-pyrazinyl	NHAc	N	N	C ₂₃ H ₂₂ FN ₇ O ₃



Compound	R1	Formula
326246	Me	C ₁₉ H ₂₂ FN ₅ O ₃
326556	H	C ₁₈ H ₂₀ FN ₅ O ₃



326241: C20 H19 F N4 O4

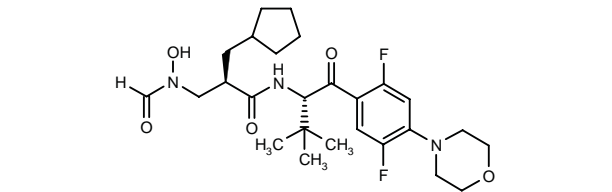
SOURCE – Ortho-McNeil.

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326501

3-Cyclopentyl-*N*-[1(*S*)-[2,5-difluoro-4-(4-morpholinyl)-benzoyl]-2,2-dimethylpropyl]-2(*R*)-(N-formyl-N-hydroxy-aminomethyl)propionamide



C26 H37 F2 N3 O5; Mol wt: 509.5903

ACTION – Antibacterial agent, an inhibitor of *Escherichia coli* peptide deformylase (IC₅₀ = 0.5 nM) with broad-spectrum antibacterial activity against respiratory tract pathogens including susceptible or resistant strains of *Streptococcus pneumoniae* (MIC = 0.25-0.5 µg/ml) and *Haemophilus influenzae* (MIC = 0.25-2 µg/ml). It was particularly active against *Moraxella catarrhalis* (MIC < 0.125 µg/ml) and exhibited a favorable pharmacokinetic profile. Selected for further *in vivo* evaluation.

SOURCE – British Biotech.

REFERENCES

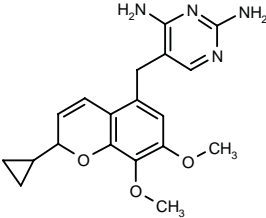
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AR-100*

253560

(±)-5-(2-Cyclopropyl-7,8-dimethoxy-2*H*-1-benzopyran-5-ylmethyl)pyrimidine-2,4-diamine

AR-101 ([*R*]-isomer)
AR-102 ([*S*]-isomer)
Ro-48-2622
Iclaprim (Rec INN)



C19 H22 N4 O3; Mol wt: 354.4078

ACTION – Antibacterial agent, a diaminopyrimidine derivative that specifically inhibits bacterial dihydrofolate reductase (DHFR), with IC₅₀ values of 2.4, 0.8 and 0.043 µM, respectively, against *Pneumocystis carinii* and mutant *Staphylococcus aureus* and *Streptococcus pneumoniae* enzymes but no activity against human enzyme (IC₅₀ > 180 µM); for comparison, trimethoprim exhibited less inhibitory activity against the bacterial enzyme (IC₅₀ = 43, 15 and 3 µM, respectively). It also potently and selectively inhibits DNA synthesis without affecting the synthesis of macromolecules. Compound exhibited good activity against Gram-positive and Gram-negative pathogens including methicillin-sensitive and -resistant strains of *S. aureus* (MIC₉₀ = 0.5 µg/ml), coagulase-negative staphylococci (MIC₅₀ = 0.25 µg/ml), *S. pneumoniae* (MIC₉₀ = 0.5 µg/ml), *Enterococcus faecalis* (including vancomycin-resistant isolates; MIC = 0.06 µg/ml), *Escherichia coli* (MIC₉₀ = 1 µg/ml), *Haemophilus influenzae* (MIC = 1 µg/ml or less), *Streptococcus pyogenes* (MIC₉₀ = 0.06 µg/ml) and *Streptococcus agalactiae* (MIC₉₀ = 0.25 µg/ml). It was more active against clinical isolates of methicillin-sensitive and -resistant *S. aureus* than the reference agents trimethoprim, ciprofloxacin, vancomycin, linezolid, erythromycin and clindamycin, and it was at least as active as the reference antibiotics against streptococci, enterococci and *H. influenzae*, but it was less active than most of the other agents against *Moraxella catarrhalis* (MIC₉₀ = 16.0 µg/ml). When tested against anaerobes, compound was slightly more active

than trimethoprim but less active than cotrimoxazole. It exhibited potent and rapid bactericidal activity against sensitive and resistant strains of *S. aureus*, streptococci and *E. faecalis*, as well as significant postantibiotic effect against Gram-positive bacteria. In mice with septicemia caused by methicillin-resistant *S. aureus*, compound significantly prolonged survival, with ED₅₀ values of 4.3 and 17.4 mg/kg following single i.v. and p.o. doses, respectively; for comparison, vancomycin gave an ED₅₀ of 0.9 mg/kg s.c.

SOURCES – Arpida; Roche.

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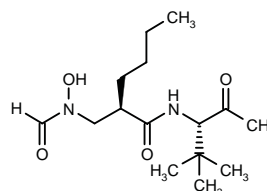
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*Identified compound **253560** (see **253027**) Drug Data Rep 1997, 019(09): 0822.

BB-83698*

296043

N-[1(*S*)-Acetyl-2,2-dimethylpropyl]-2(*R*)-(N-formyl-*N*-hydroxyaminomethyl)hexanamide



C15 H28 N2 O4; Mol wt: 300.3962

ACTION – Broad-spectrum antibacterial agent, an inhibitor of peptide deformylase (PDF; IC₅₀ = 10 nM against *Escherichia coli* enzyme) with excellent activity against *Streptococcus pneumoniae* (MIC₉₀ = 0.12-0.5 µg/ml) and *Moraxella catarrhalis* (MIC₉₀ = 0.015-0.12 µg/ml), and moderate activity against *Haemophilus influenzae* (MIC₉₀ = 0.5-16 µg/ml). It was also active against atypical respiratory pathogens such as *Legionella pneumophila* and *Mycoplasma pneumoniae* (MIC₉₀ = 1 and 0.004 µg/ml, respectively). Compound showed a lower likelihood for the development of resistance compared to actinonin and ciprofloxacin following serial passage in *S. pneumoniae* ATCC 49619. In a mouse model of pneumonia caused by *S. pneumoniae*, a dose of 80 mg/kg s.c. b.i.d. showed good efficacy in protecting against death and no emergence of resistance to *S. pneumoniae* isolates was observed after suboptimal treatment. Currently in phase I clinical trials for the treatment of community-acquired pneumonia.

SOURCES – British Biotech; GeneSoft.

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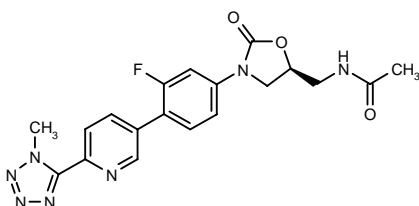
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*Identified compound **296043** (see **296036**) Drug Data Rep 2001, 023(03): 0277.

DA-7867*

314265

N-[3-[3-Fluoro-4-[6-(1-methyl-1H-tetrazol-5-yl)pyridin-5-yl]phenyl]-2-oxooxazolidin-5(S)-ylmethyl]acetamide



C19 H18 F N7 O3; Mol wt: 411.3952

ACTION – Pyridine-containing oxazolidinone antibacterial agent with at least 4-fold higher activity than linezolid against Gram-positive and Gram-negative bacteria including multidrug-resistant strains such as methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus faecium* (VRE), penicillin-resistant *Streptococcus pneumoniae* (PRSP), *Haemophilus influenzae* and *Moraxella catarrhalis* (MIC₉₀ = 0.78, 0.2, 0.39, 3.13 and 0.78 µg/ml, respectively). It was also active against aerobic and anaerobic Gram-positive isolates including multidrug-resistant strains, with MIC₉₀ values of 0.25 and 0.5 µg/ml or less, respectively. *In vivo*, compound was approximately 2-fold more potent than linezolid against systemic infections in mice caused by *S. aureus*, MRSA, *S. pneumoniae*, PRSP and VRE (ED₅₀ = 3.4, 2.6, 11.6, 2.4 and 4.5 mg/kg p.o., respectively), and it was much more effective than linezolid against respiratory tract infections caused by PRSP and in the pouch model of infection with MRSA. Compound exhibited more favorable pharmacokinetics than linezolid, with a longer half-life (5.56 and 12.4 h in mice and rats, respectively) and higher oral bioavailability (91 and 54% in mice and rats, respectively).

SOURCE – Dong-A.

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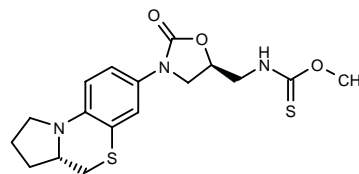
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*Identified compound **314265** (see **314261**) Drug Data Rep 2002, 024(03): 0251.

DRL-11286

325686

N-[3-[(3aS)-2,3,3a,4-Tetrahydro-1H-pyrrolo[2,1-c][1,4]-benzothiazin-7-yl]-2-oxooxazolidin-5(S)-ylmethyl]thiocarbamic acid O-methyl ester



C17 H21 N3 O3 S2; Mol wt: 379.5029

ACTION – Conformationally constrained oxazolidinone antibacterial active against Gram-positive microorganisms including sensitive and resistant strains of *Staphylococcus aureus*, *Enterococcus faecalis* and *Enterococcus faecium* (MIC = 0.25-1 µg/ml).

SOURCE – Dr. Reddy's Laboratories.

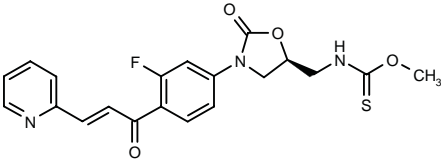
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DRL-12035

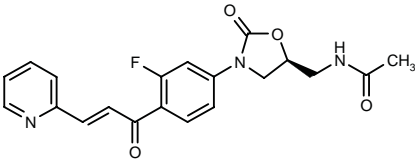
325689

N-[3-[3-Fluoro-4-[3-(2-pyridyl)-2-propenoyl]phenyl]-2-oxooxazolidin-5(*S*)-ylmethyl]thiocarbamic acid *O*-methyl ester



C20 H18 F N3 O4 S; Mol wt: 415.4432

ACTION – Antibacterial agent, a chalcone–oxazolidinone hybrid with excellent antibacterial activity against Gram-positive bacteria including drug-resistant strains such as methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus faecalis* and vancomycin-resistant *Enterococcus faecium* (MIC = 0.25, 1 and 2 µg/ml respectively). Another related compound is:



DRF-8129 [325688]: C20 H18 F N3 O4

SOURCE – Dr. Reddy’s Laboratories.

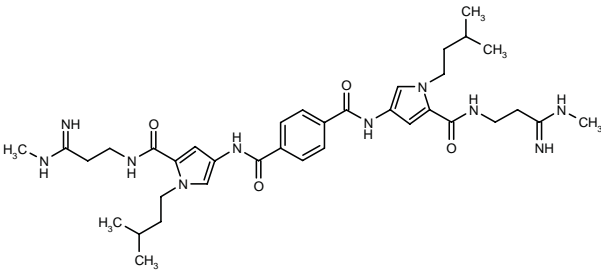
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GL-579225*,1,3,4,5

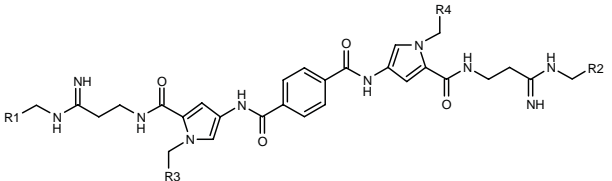
314998

N,N'-Bis[5-[*N*-[2-(*N*¹-methylamidino)ethyl]carbamoyl]-1-(3-methylbutyl)-1*H*-pyrrol-3-yl]benzene-1,4-dicarboxamide



C36 H52 N10 O4; Mol wt: 688.8728

ACTION – Antibacterial agent, a pyrrole tetraamide with nanomolar DNA binding affinity and strong *in vitro* activity against vancomycin-resistant enterococci and methicillin-resistant *Staphylococcus aureus* (MIC₉₀ = 1.06 and 0.53 µg/ml, respectively). In a neutropenic mouse model of thigh infection caused by methicillin-resistant or -sensitive *S. aureus*, compound at doses of 5 and 10 mg/kg exhibited bactericidal activity, with 2 log greater potency than vancomycin. Other related compounds are:



Compound	R1=R2	R3=R4	Formula
GL-521997 [312943] ^{1-3,5}	Pr	cyclopropyl	C ₄₀ H ₅₆ N ₁₀ O ₄
GL-548043 [324113] ^{3,5}	Me	i-Pr	C ₃₈ H ₅₂ N ₁₀ O ₄
GL-568816 [325494] ^{3,5}	H	cyclobutyl	C ₃₈ H ₄₈ N ₁₀ O ₄

SOURCE – Genelabs.

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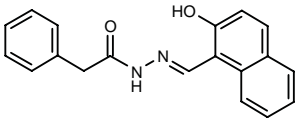
*Identified compound **314998** (see **GL-757899**) Drug Data Rep 2002, 024(03): 0252.

INF-401

327048

Phenylacetic acid *N'*-(2-hydroxy-1-naphthylmethylene)-hydrazide

INF BCP



C19 H16 N2 O2; Mol wt: 304.3474

ACTION – Bactericidal potentiator of bacteriostatic antibiotics that lacks intrinsic antibacterial activity but synergistically imparts bactericidal activity to erythromycin, chloramphenicol, tetracycline, linezolid, clindamycin or rifampin, and strongly decreases the minimum bactericidal concentration (MBC) of these antibiotics against *Staphylococcus aureus*. The compound alone produced an accumulation of iron inside the cell, leading to increased levels of reactive oxygen species and thereby increasing the production of several antioxidant proteins; however, in combination with antibiotics affecting protein synthesis, the synthesis of antioxidant proteins is inhibited, leading to a rapid degradation of bacterial DNA and bacterial death. *In vivo*, compound was well tolerated by mice at up to 30 mg/kg i.v.

SOURCE – Influx.

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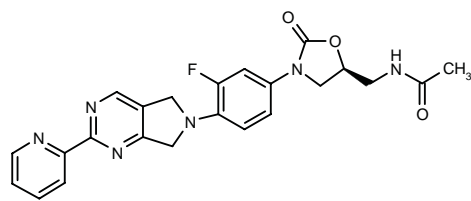
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JNJ-10391849

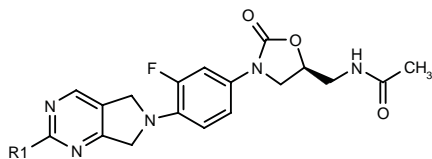
325581

N-[3-[3-Fluoro-4-[2-(2-pyridyl)-5,7-dihydro-6H-pyrrolo-[3,4-*d*]pyrimidin-6-yl]phenyl]-2-oxooxazolidin-5(*S*)-yl-methyl]acetamide



C23 H21 F N6 O3; Mol wt: 448.4559

ACTION – Pyrrolopyrimidine oxazolidinone with antibacterial activity comparable to linezolid against methicillin-sensitive and -resistant *Staphylococcus aureus*, vancomycin-susceptible *Enterococcus faecalis* and vancomycin-resistant *Enterococcus faecium* (MIC = 2 µg/ml). Compound also exhibited *in vivo* efficacy comparable to linezolid against septicemia caused by *S. aureus* in mice (ED₅₀ = 11 mg/kg s.c.). Other related compounds are:



Compound	R1	Formula
JNJ-10266217 [325580]	Me	C ₁₉ H ₂₀ FN ₅ O ₃
JNJ-10283104 [325582]	3-Pyr	C ₂₃ H ₂₁ FN ₆ O ₃

SOURCE – Johnson & Johnson.

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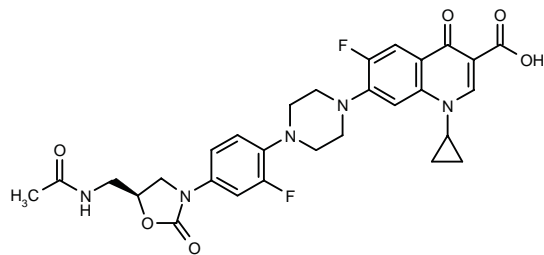
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MCB-116*

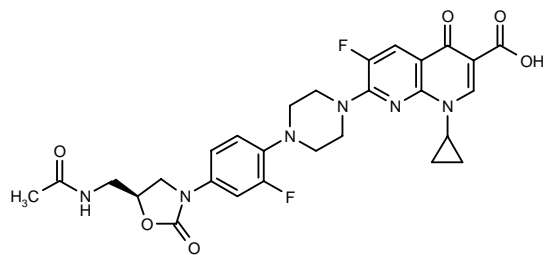
324984

7-[4-[4-[5(*S*)-(Acetamidomethyl)-2-oxooxazolidin-3-yl]-2-fluorophenyl]piperazin-1-yl]-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid

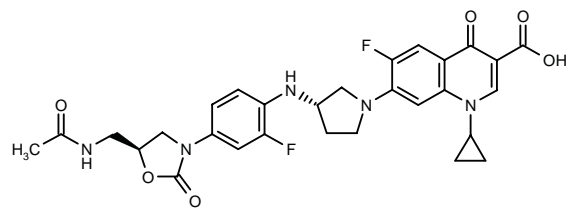


C29 H29 F2 N5 O6; Mol wt: 581.5731

ACTION – Quinolone-linked oxazolidinone antibacterial agent with 4-16-fold improved potency compared to linezolid against Gram-positive and fastidious Gram-negative bacteria including strains that developed resistance to linezolid. MIC₉₀ values against clinical isolates of staphylococci, enterococci, streptococci and enterococci were 0.03-0.5 µg/ml. It acts primarily as an inhibitor of protein synthesis (IC₅₀ = 2.8 µM in a transcription/translation assay), although it exhibited weak activity against DNA gyrase (IC₅₀ = 20 µM). Preliminary studies in rats suggested acceptable pharmacokinetic properties for the compound. Other related compounds are:



MCB-2038 [325268]: C28 H28 F2 N6 O6



MCB-1033 [325270]: C29 H29 F2 N5 O6

SOURCES – Morphochem; Pharmacia.

REFERENCES

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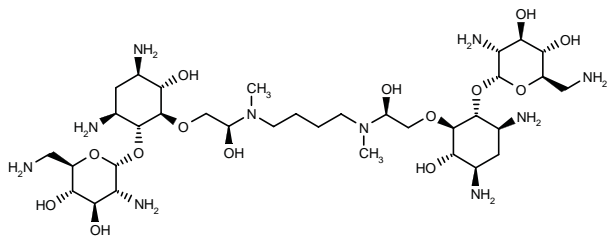
2. Locher, H.H. et al. *Synthesis and antibacterial action of novel quinolone-linked oxazolidinones*. 42nd Intersci Conf Antimicrob Agents Chemother (Sept 27-30, San Diego) 2002, Abst F-1317.

*Identified compound **324984** Drug Data Rep 2002, 024(10): 0915.

OPT-11

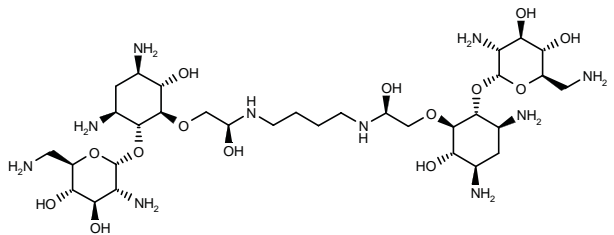
325577

1-*O*,1'-*O*-(Butane-1,4-diyl)bis(methylimino)bis[1(*S*)-hydroxyethylene]bis(oxy)bis[4(*R*),6(*S*)-diamino-3(*S*)-hydroxycyclohexan-2(*R*),1(*R*)-diyl]bis(2,6-diamino-2,6-dideoxy- α -D-glucopyranose)



C34 H72 N10 O14; Mol wt: 844.9988

ACTION – Antibacterial agent, a multivalent aminoglycoside active against multidrug-resistant *Pseudomonas aeruginosa* clinical isolates and laboratory strains of *Staphylococcus aureus* and *Escherichia coli* (MIC = 1-16 µg/ml). It showed improved activity relative to tobramycin against aminoglycoside-resistant strains of *P. aeruginosa*. *In vivo*, compound was effective in protecting mice from lethal infection due to *S. aureus* with an ED₅₀ < 5 mg/kg i.v. Another related compound is:



325579: C32 H68 N10 O14

SOURCE – Optimer Pharmaceuticals.

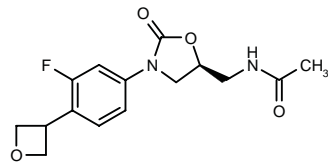
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PNU-293180

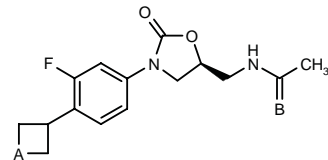
325570

N-[3-[3-Fluoro-4-(3-oxetanyl)phenyl]-2-oxooxazolidin-5(*S*)-ylmethyl]acetamide



C15 H17 F N2 O4; Mol wt: 308.3073

ACTION – Oxazolidinone antibacterial agent with activity comparable to linezolid against sensitive and resistant strains of Gram-positive and Gram-negative bacteria including methicillin-sensitive and -resistant *Staphylococcus aureus* (MIC = 2 µg/ml), methicillin-resistant *Staphylococcus epidermidis* (MIC = 2 µg/ml), penicillin-susceptible *Streptococcus pneumoniae* (MIC = 1 µg/ml) and vancomycin-susceptible *Enterococcus faecalis* (MIC = 2 µg/ml). It was 2-fold less active than linezolid against *Haemophilus influenzae* (MIC = 16 and 8 µg/ml, respectively). Compound exhibited oral activity comparable to linezolid against murine systemic infections induced by *S. aureus* (ED₅₀ = 1.2 and 1.6 mg/kg, respectively). Other related compounds are:



Compound	A	B	Formula
PNU-290870 [325565]	-S-	O	C ₁₅ H ₁₇ FN ₂ O ₃ S
PNU-291899 [325566]	-SO ₂ -	O	C ₁₅ H ₁₇ FN ₂ O ₅ S
PNU-291956 [325567]	-S-	S	C ₁₅ H ₁₇ FN ₂ O ₂ S ₂
PNU-291654 [325569]	-SO-	O	C ₁₅ H ₁₇ FN ₂ O ₄ S
PNU-294580 [325572]	-O-	S	C ₁₅ H ₁₇ FN ₂ O ₃ S

SOURCE – Pharmacia.

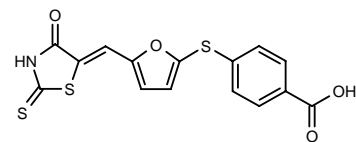
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PTX-008134

327040

(*Z*)-4-[5-(4-Oxo-2-thioxothiazolidin-5-ylidenemethyl)-2-furylsulfanyl]benzoic acid



C15 H9 N O4 S3; Mol wt: 363.4371

ACTION – Potential antibacterial agent that selectively inhibits bacterial phosphopantetheine adenylyltransferase (PPAT) versus human enzyme.

SOURCE – PanTherix.

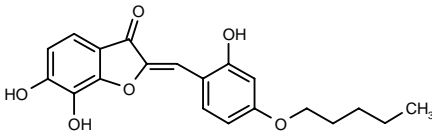
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PTX-008313

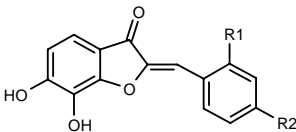
325696

(Z)-6,7-Dihydroxy-2-[2-hydroxy-4-(pentyloxy)benzylidene]-1-benzofuran-3(2H)-one



C20 H20 O6; Mol wt: 356.3720

ACTION – Potential antibacterial agent, an inhibitor of chorismate synthase, an enzyme in the shikimate pathway essential for the synthesis of aromatic acids in bacteria. It inhibited chorismate synthase from *Streptococcus pneumoniae* and *Enterococcus faecalis* with respective IC₅₀ values of 0.22 and 0.81 μM. Other related compounds are:



Compound	R1	R2	Formula
PTX-110130 [325692]	H	N(Et)2	C ₁₉ H ₁₉ NO ₄
PTX-008218 [325698]	OH	H	C ₁₅ H ₁₀ O ₅
PTX-008330 [325699]	OH	OPr	C ₁₈ H ₁₆ O ₆

SOURCE – PanTherix.

REFERENCES

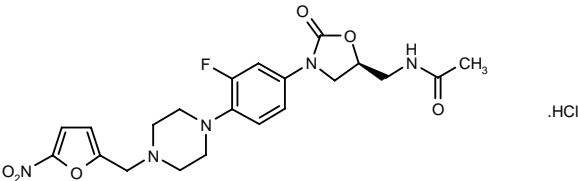
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RANBEZOLID HYDROCHLORIDE*

316064

N-[3-[3-Fluoro-4-[4-(5-nitrofuran-2-ylmethyl)piperazin-1-yl]phenyl]-2-oxooxazolidin-5(S)-ylmethyl]acetamide hydrochloride

RBx-7644



C21 H24 F N5 O6 . HCl; Mol wt: 497.9085

ACTION – Extended-spectrum oxazolidinone antibacterial agent active against Gram-positive and Gram-negative anaerobes (MIC₉₀ = 0.28-0.5 μg/ml), Gram-positive pathogens including multidrug-resistant strains (MIC₉₀ = 2 μg/ml), as well as *Mycobacterium tuberculosis*, *Moraxella catarrhalis* and certain strains of *Haemophilus influenzae* and *Neisseria gonorrhoeae* (MIC = 2-32 μg/ml). It was more active than linezolid against methicillin-resistant staphylococci, particularly coagulase-negative strains (MIC₉₀ = 1-2 μg/ml). Pharmacokinetics were linear and proportional to dose; no accumulation was seen following repeated doses. Subacute toxicity studies in rats showed that compound at 20-125 mg/kg/day p.o. for 28 days was well tolerated, with a no-effect dose of 50 mg/kg/day.

SOURCE – Ranbaxy.

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5. Koppolu, K. et al. *In vitro activity of RBx 7644, a novel oxazolidinone, against anaerobic bacteria*. 6th Int Conf Macrolides Azalides Streptogramins Ketolides Oxazolidinones (Jan 23-25, Bologna) 2002, Abst 1.10.

6. Malhotra, S. et al. *Determining the PK/PD parameter correlating with efficacy of RBx 7644*. 6th Int Conf Macrolides Azalides Streptogramins Ketolides Oxazolidinones (Jan 23-25, Bologna) 2002, Abst 1.15.

7. Malhotra, S. et al. *Efficacy of RBx 7644 in a murine pouch model of infection caused by methicillin resistant Staphylococcus aureus and Streptococcus pneumoniae*. 6th Int Conf Macrolides Azalides Streptogramins Ketolides Oxazolidinones (Jan 23-25, Bologna) 2002, Abst 5.11.

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11. Pandya, M. et al. *Effect of pH, inoculum size, serum and albumin on antibacterial activity of RBx 7644*. 6th Int Conf Macrolides Azalides Streptogramins Ketolides Oxazolidinones (Jan 23-25, Bologna) 2002, Abst 1.11.

12. Pandya, M. et al. *Investigational oxazolidinone RBx 7644 is active against adherent bacteria*. 6th Int Conf Macrolides Azalides Streptogramins Ketolides Oxazolidinones (Jan 23-25, Bologna) 2002, Abst 1.08.

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15. Rattan, A. et al. *In vitro susceptibility breakpoint determination for RBx 7644*. 42nd Intersci Conf Antimicrob Agents Chemother (Sept 27-30, San Diego) 2002, Abst F-1294.

16. Shingatgeri, V.M. et al. *Subacute toxicity of RBx 7644 by oral route in rats*. 42nd Intersci Conf Antimicrob Agents Chemother (Sept 27-30, San Diego) 2002, Abst F-1300.

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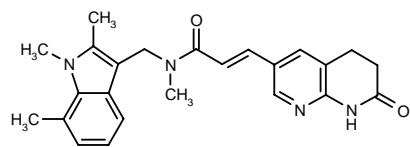
20. *Research and development*. Ranbaxy Laboratories Web Site 2002, Oct 25.

*Identified compound **316064** Drug Data Rep 2002, 024(04): 0345.

SB-663042

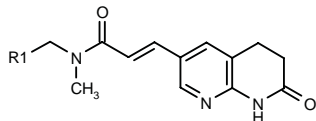
327046

N-Methyl-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)-*N*-(1,2,7-trimethyl-1*H*-indol-3-ylmethyl)-2(*E*)-propenamide



C24 H26 N4 O2; Mol wt: 402.4954

ACTION – Antibacterial agent, an inhibitor of *Staphylococcus aureus* FabI (IC₅₀ < 3 nM) with potent antibacterial activity against triclosan-resistant *S. aureus* strains (MIC < 0.001-0.016 µg/ml). Other related compounds are:



Compound	R1	Formula
SB-627696 [327045]	1,2-(Me)2-3-indolyl	C ₂₃ H ₂₄ N ₄ O ₂
SB-633857 [327047]	3-Me-2-benzothieryl	C ₂₂ H ₂₁ N ₃ O ₂ S

SOURCE – GlaxoSmithKline.

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2. Payne, W.J. et al. *Discovery of FabI inhibitors active against triclosan resistant strains of Staphylococcus aureus*. 42nd Intersci Conf Antimicrob Agents Chemother (Sept 27-30, San Diego) 2002, Abst F-751.

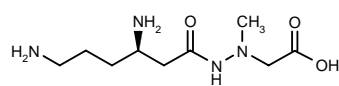
VRC-3573¹⁻³

325665

2-[2-[3(*R*),6-Diaminohexanoyl]-1-methylhydrazino]acetic acid

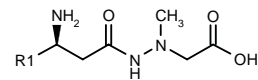
3(*R*),6-Diaminohexanoic acid 2-(carboxymethyl)-2-methylhydrazide

Deoxynegamycin



C9 H20 N4 O3; Mol wt: 232.2820

ACTION – Antibacterial agent, an analogue of negamycin that inhibited bacterial (*Escherichia coli*) protein synthesis with an IC₅₀ of 8.2 µM and showed significant antibacterial activity against *E. coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae* (MIC = 4-16 µg/ml) and *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Streptococcus pneumoniae* (MIC = 64 µg/ml). *In vivo*, it was more effective than ampicillin in protecting mice from septicemia induced by *E. coli* (ED₅₀ = 4.8 and 10 mg/kg i.v., respectively). Other related compounds are:



Compound	R1	Formula
VRC-4902 [325666]	3-Pip	C ₁₁ H ₂₂ N ₄ O ₃
VRC-4851 [325667]	2-NH2-cyclopropyl	C ₉ H ₁₈ N ₄ O ₃

SOURCE – Versicor.

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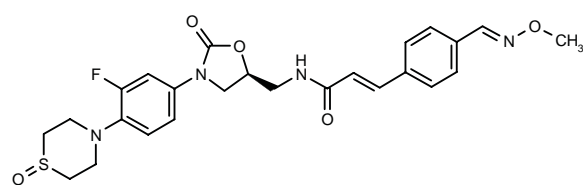
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VRC-3885

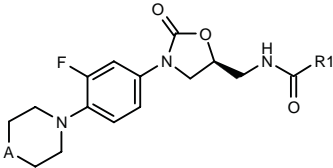
325680

N-[3-[3-Fluoro-4-(1-oxothiomorpholin-4-yl)phenyl]-2-oxo-oxazolidin-5(*S*)-ylmethyl]-3-[4-(methoxyiminomethyl)-phenyl]-2-propenamide



C25 H27 F N4 O5 S; Mol wt: 514.5753

ACTION – Oxazolidinone antibacterial agent with good activity against methicillin-resistant *Staphylococcus aureus*, methicillin-resistant *Staphylococcus epidermidis*, vancomycin-resistant *Enterococcus faecium* and *Streptococcus pneumoniae* (MIC = 1-2, 1, 2 and 0.5 µg/ml, respectively). Other related compounds are:



Compound	R1	A	Formula
VRC-3883 [325678]	4-Cl-PhCH=CH	SO	C ₂₃ H ₂₃ ClFN ₃ O ₄ S
VRC-7047 [325681]	CHF2	SO2	C ₁₆ H ₁₈ F ₃ N ₃ O ₅ S

SOURCE – Versicor.

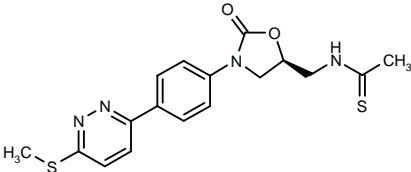
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VRC-4228

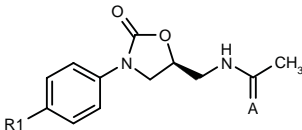
325694

N-[3-[4-[6-(Methylsulfanyl)pyridazin-3-yl]phenyl]-2-oxooxazolidin-5(*S*)-ylmethyl]thioacetamide



C17 H18 N4 O2 S2; Mol wt: 374.4872

ACTION – Phenyloxazolidinone antibacterial agent with an expanded spectrum of activity compared to linezolid, showing high activity against Gram-positive and Gram-negative microorganisms including *Staphylococcus aureus* (MIC = 0.25-0.5 µg/ml), *Staphylococcus epidermidis* (MIC = 0.125-0.25 µg/ml), vancomycin-resistant *Enterococcus faecium* (MIC = 0.25 µg/ml), *Streptococcus pneumoniae* (MIC = 0.125 µg/ml), *Haemophilus influenzae* (MIC = 2-4 µg/ml) and *Moraxella catarrhalis* (MIC = 0.5 µg/ml). Other related compounds are:



Compound	R1	A	Formula
VRC-4282 [325691]	6-oxo-1,6-dihydro-3-pyridazinyl	S	C ₁₆ H ₁₆ N ₄ O ₃ S
VRC-4189 [325693]	6-thioxo-1,6-dihydro-3-pyridazinyl	S	C ₁₆ H ₁₆ N ₄ O ₂ S ₂
VRC-4437 [325695]	6-(MeSO2)-3-pyridazinyl	O	C ₁₇ H ₁₈ N ₄ O ₅ S

SOURCE – Versicor.

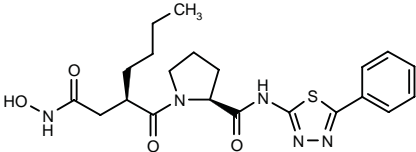
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VRC-4408

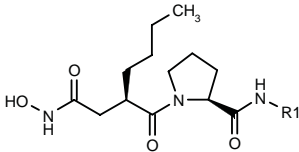
325675

1-[2(*R*)-(N-Hydroxycarbamoylmethyl)hexanoyl]-*N*-(5-phenyl-1,3,4-thiadiazol-2-yl)-L-prolinamide



C21 H27 N5 O4 S; Mol wt: 445.5413

ACTION – Antibacterial agent, a chelator-based inhibitor of bacterial peptide deformylase (IC₅₀ = 0.021 µM against *Escherichia coli* enzyme) with strong antibacterial activity against *Streptococcus pneumoniae*, *Staphylococcus aureus* and *Haemophilus influenzae* (MIC = 0.06-0.25, 0.06-0.25 and 0.5-42 µg/ml, respectively). It also showed significant cytotoxicity against K-562 cells (IC₅₀ = 0.09 µM). Other related compounds are:



Compound	R1	Formula
VRC-4398 [325670]	4-Me-2-thiazolyl	C ₁₇ H ₂₆ N ₄ O ₄ S
VRC-4404 [325671]	4,5-(Me)2-2-thiazolyl	C ₁₈ H ₂₈ N ₄ O ₄ S
VRC-4405 [325672]	2-benzothiazolyl	C ₂₀ H ₂₆ N ₄ O ₄ S
VRC-4406 [325673]	4-Ph-2-thiazolyl	C ₂₂ H ₂₈ N ₄ O ₄ S
VRC-4407 [325674]	3-(PhO)-Ph	C ₂₅ H ₃₁ N ₃ O ₅

SOURCE – Versicor.

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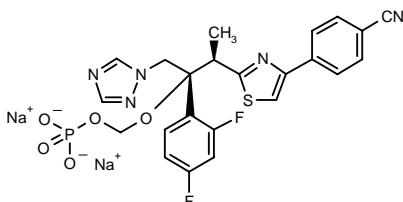
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ANTIFUNGAL AGENTS

BMS-379224^{2,3,5,6}

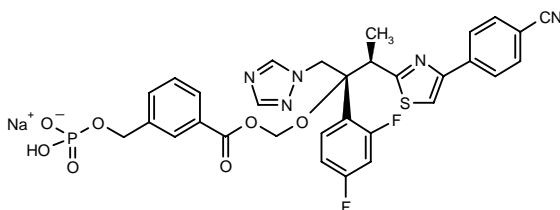
309048

2(*R*)-[4-(4-Cyanophenyl)thiazol-2-yl]-1(*R*)-(2,4-difluorophenyl)-1-(1*H*-1,2,4-triazol-1-ylmethyl)propoxymethyl dihydrogen phosphate disodium salt



C23 H18 F2 N5 Na2 O5 P S; Mol wt: 591.4412

ACTION – Phosphonooxymethyl ether prodrug of ravuconazole with improved water solubility and stability in solid and solution forms, readily converted in 1 step to the parent compound *in vitro* and *in vivo* following i.v. administration to rats, dogs and monkeys. *In vitro*, it was much less active than the parent drug; *in vivo*, in mice with systemic *Candida albicans* infection, the prodrug was rapidly converted to ravuconazole, providing similar plasma levels to orally administered parent drug; the two compounds were equipotent in this model. Another less efficient prodrug of ravuconazole requiring 2-step hydrolysis is:



BMS-292655 [325495]^{1,4}: C31 H25 F2 N5 Na O7 P S

SOURCE – Bristol-Myers Squibb.

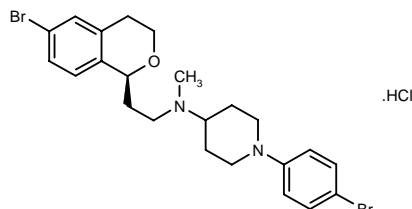
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- Hudyma, T.W. et al. *BMS-292655, a soluble prodrug of the clinically efficacious antifungal triazole, BMS-207147 (ravuconazole).* 42nd Intersci Conf Antimicrob Agents Chemother (Sept 27-30, San Diego) 2002, Abst F-816.
- Ueda, Y. et al. *BMS-379224, a water-soluble prodrug of ravuconazole.* 42nd Intersci Conf Antimicrob Agents Chemother (Sept 27-30, San Diego) 2002, Abst F-817.
- Webb, C.D. et al. *In vitro and in vivo microbiological evaluation of the ravuconazole prodrug, BMS-379224.* 42nd Intersci Conf Antimicrob Agents Chemother (Sept 27-30, San Diego) 2002, Abst F-818.

PNU-271965E

327043

N-[2-[6-Bromo-3,4-dihydro-1*H*-2-benzopyran-1(*S*)-yl]ethyl]-1-(4-bromophenyl)-*N*-methylpiperidin-4-amine hydrochloride



C23 H28 Br2 N2 O . HCl; Mol wt: 544.7561

ACTION – Antifungal agent, an inhibitor of fungal glucan synthase, with selectivity over chitin synthase, trehalose-6-phosphate synthase or plasma H⁺-ATPase. It exhibited broad-spectrum antifungal activity against *Candida albicans*, *Candida glabrata*, *Candida krusei*, *Candida parapsilosis*, *Aspergillus fumigatus* and *Aspergillus terreus* (MIC = 0.25-0.32 µg/ml) and showed fungicidal activity against *C. albicans*, *C. krusei* and *A. fumigatus*. Good monolayer permeability in Caco-2 human colon adenocarcinoma cells was seen, consistent with good oral bioavailability in mice.

SOURCE – Pharmacia.

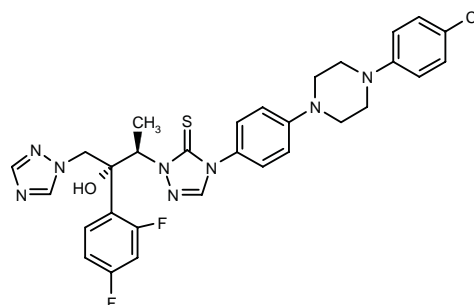
REFERENCES

- Wilks, J. et al. *Unique inhibitors of fungal glucan synthase.* 42nd Intersci Conf Antimicrob Agents Chemother (Sept 27-30, San Diego) 2002, Abst F-829.

RBx-7635*

323763

4-[4-[4-(4-Chlorophenyl)piperazin-1-yl]phenyl]-2-[2(*R*)-(2,4-difluorophenyl)-2-hydroxy-1(*R*)-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-3,4-dihydro-2*H*-1,2,4-triazole-3-thione



C30 H29 Cl F2 N8 O S; Mol wt: 623.1291

ACTION – Thiotriazolone antifungal agent with excellent *in vitro* activity against *Candida parapsilosis* (MIC < 0.00025 µg/ml), *Cryptococcus neoformans* (MIC < 0.00025 µg/ml), *Candida tropicalis* (MIC = 0.002 µg/ml), *Candida albicans* (MIC = 0.125 µg/ml) and fluconazole-resistant *Aspergillus fumigatus* (MIC = 0.125-0.25 µg/ml). *In vivo*, compound was highly effective in protecting mice against systemic infections caused by *C. albicans* (ED₅₀ = 2.86-10.51 mg/kg p.o.) and *A. fumigatus* (ED₅₀ = 6.25 mg/kg p.o.).

SOURCE – Ranbaxy.

REFERENCES

1. Salman, M. et al. (Ranbaxy Laboratories Ltd.) *Azole cpds. as anti-fungal agents*. WO 0251408.

2. Salman, M. et al. *Thiotriazolones: A new class of potent antifungal agents*. 42nd Intersci Conf Antimicrob Agents Chemother (Sept 27-30, San Diego) 2002, Abst F-828.

3. *Research and development*. Ranbaxy Laboratories Web Site 2002, Jan 29.

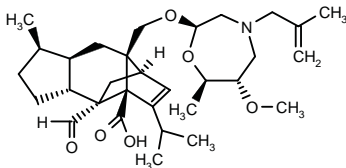
4. *Research and development*. Ranbaxy Laboratories Web Site 2002, Oct 25.

*Identified compound **323763** (see **323627**) Drug Data Rep 2002, 024(09): 0820.

RS-135853*

322899

(1*R*,3*aR*,4*S*,4*aR*,7*R*,7*aR*,8*aS*)-4-Formyl-3-isopropyl-8a-[(2*R*,6*S*,7*R*)-6-methoxy-7-methyl-4-(2-methyl-2-propenyl)perhydro-1,4-oxazepin-2-yloxymethyl]-7-methyl-4,4*a*,5,6,7,7*a*,8,8*a*-octahydro-1*H*-1,4-methano-*s*-indacene-3*a*-carboxylic acid



C31 H47 N O6; Mol wt: 529.7133

ACTION – Antifungal agent, a zofimarin derivative with excellent, broad-spectrum *in vitro* activity against *Candida albicans*, *Candida glabrata* and *Candida tropicalis* (MIC = 0.016-0.03, 0.06 and 0.5 µg/ml, respectively), but little or no activity against *Candida parapsilosis*, *Candida krusei* and *Aspergillus* spp. *In vivo*, it exhibited excellent activity after both s.c. and oral administration in murine models of systemic, oropharyngeal and esophageal candidiasis including fluconazole-resistant infections.

SOURCE – Sankyo.

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1. Kaneko, S. et al. (Sankyo Co., Ltd.) *Zofimarin derivs. having an oxazepan ring*. JP 2002161086.

2. Fukuoka, T. et al. *Design, synthesis, and in vitro activity of RS-135853, a novel zofimarin-related antifungal agent*. 42nd Intersci Conf Antimicrob Agents Chemother (Sept 27-30, San Diego) 2002, Abst F-824.

3. Fukuoka, T. et al. *In vivo antifungal activity of RS-135853, a novel zofimarin-related antifungal agent*. 42nd Intersci Conf Antimicrob Agents Chemother (Sept 27-30, San Diego) 2002, Abst F-825.

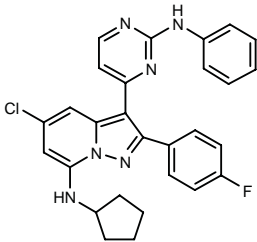
4. Kaneko, S. et al. *Synthesis and evaluation of N-substituted 1,4-oxazepanyl sordarinics as selective fungal EF-2 inhibitors*. Bioorg Med Chem Lett 2002, 12(13): 1705.

*Identified compound **322899** Drug Data Rep 2002, 24(10): 917.

ANTIVIRAL DRUGS

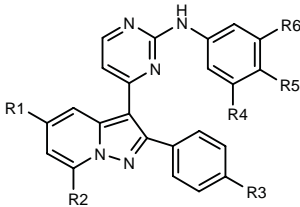
323162

5-Chloro-*N*-cyclopentyl-2-(4-fluorophenyl)-3-[2-(phenylamino)pyrimidin-4-yl]pyrazolo[1,5-*a*]pyridin-7-amine



C28 H24 Cl F N6; Mol wt: 498.9906

ACTION – Agent for the treatment of herpesvirus infections caused by herpes simplex virus type 1 (HSV-1) and 2 (HSV-2), cytomegalovirus, Epstein-Barr virus, varicella-zoster virus and human herpesvirus HHV-6, HHV-7 and HHV-8. Compound prevented the infectivity of HSV-1 in Vero cells with an IC₅₀ value of 0.16 µM. Other exemplified compounds are:



Compound	R1	R2	R3	R4	R5	R6	Formula
323163	H	cyclopentyl-NH	F	H	H	H	C ₂₈ H ₂₅ FN ₆
323164	H	cyclopentyl-NH	F	OMe	OMe	OMe	C ₃₁ H ₃₁ FN ₆ O ₃
323165	H	cyclopentyl-NH	F	H	OMe	H	C ₂₉ H ₂₇ FN ₆ O
323166	H	cyclopentyl-NH	F	H	F	H	C ₂₈ H ₂₄ F ₂ N ₆
323167	H	cyclopentyl-NH	OMe	H	H	COPh	C ₃₆ H ₃₂ N ₆ O ₂
323168	Cl	H	F	H	H	H	C ₂₃ H ₁₅ ClFN ₅
323169	cyclopentyl-NH	H	F	H	H	H	C ₂₈ H ₂₅ FN ₆
323170	Cl	SEt	F	H	H	H	C ₂₈ H ₁₉ ClFN ₅ S
323180	H	cyclopentyl-NH	OMe	H	H	NO ₂	C ₂₉ H ₂₇ N ₇ O ₃
323181	H	cyclopentyl-NH	OMe	H	H	CH ₂ OH	C ₃₀ H ₃₀ N ₆ O ₂
323182	H	cyclopentyl-NH	OMe	H	H	NH ₂	C ₂₉ H ₂₉ N ₇ O
323183	H	cyclopentyl-NH	OMe	H	H	N ₃	C ₂₉ H ₂₇ N ₉ O

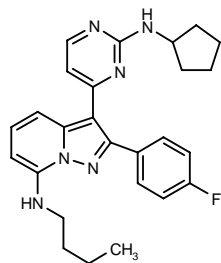
SOURCE – GlaxoSmithKline.

REFERENCES

1. Chamberlain, S.D. et al. (Glaxo Group Ltd.) *Therapeutic cpds*. WO 0248147.

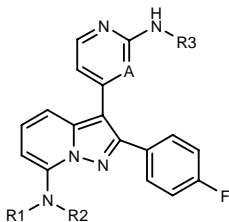
323184

N-Butyl-3-[2-(cyclopentylamino)pyrimidin-4-yl]-2-(4-fluorophenyl)pyrazolo[1,5-*a*]pyridin-7-amine



C26 H29 F N6; Mol wt: 444.5551

ACTION – Agent for the treatment of herpesvirus infections caused by herpes simplex virus type 1 (HSV-1) and 2 (HSV-2), cytomegalovirus, Epstein-Barr virus, varicella-zoster virus and human herpesvirus HHV-6, HHV-7 and HHV-8. Compound prevented the infectivity of HSV-1 in Vero cells with an IC₅₀ value of 0.2 µM. Other exemplified compounds are:



Compound	R1	R2	R3	A	Formula
323185	cyclopentyl	H	cyclopentyl	N	C ₂₇ H ₂₉ FN ₆
323186	Bu	H	Bu	N	C ₂₅ H ₂₉ FN ₆
323187	cyclopentyl	H	H	N	C ₂₂ H ₂₁ FN ₆
323188	cyclopentyl	H	cyclopentyl	CH	C ₂₈ H ₃₀ FN ₆
323190	Me	Me	Bu	N	C ₂₃ H ₂₅ FN ₆
323191	4-morpholinyl-CH2CH2	H	Bu	N	C ₂₇ H ₃₂ FN ₇ O
323192	CH2CH2OMe	H	Bu	N	C ₂₄ H ₂₇ FN ₆ O
323193	allyl	H	Bu	N	C ₂₄ H ₂₅ FN ₆

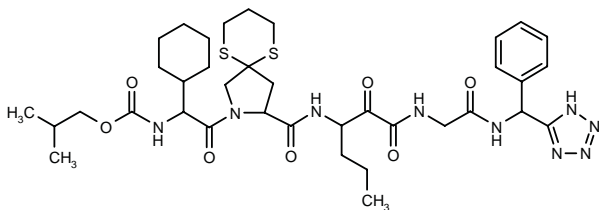
SOURCE – GlaxoSmithKline.

REFERENCES

1. Boyd, F.L. et al. (Glaxo Group Ltd.) *Therapeutic cpds.* WO 0248148.

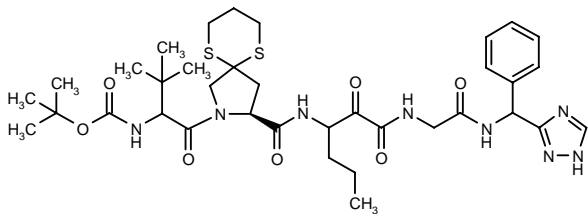
323272

N-[1-Cyclohexyl-2-oxo-2-[3-[N-[1-[2-[N-[1-phenyl-1-(1*H*-tetrazol-5-yl)methyl]carbamoylmethylamino]oxalyl]butyl]-carbamoyl]-6,10-dithia-2-azaspiro[4.5]dec-2-yl]ethyl]-carbamic acid isobutyl ester



C37 H53 N9 O7 S2; Mol wt: 800.0137

ACTION – Hepatitis C virus (HCV) NS3/NS4a serine protease inhibitor (K_i < 100 nM), potentially useful for the treatment of HCV infection. Another exemplified diaryl peptide is:



323273: C36 H52 N8 O7 S2

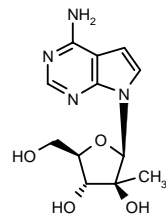
SOURCE – Schering-Plough.

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1. Zhu, Z. et al. (Schering Corp.) *Diaryl peptides as NS3-serine protease inhibitors of hepatitis C virus.* WO 0248172.

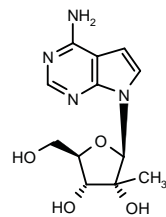
324682

7-(1-Deoxy-2-*C*-methyl-β-*D*-arabinofuranosyl)-7*H*-pyrrolo-[2,3-*d*]pyrimidin-4-amine



C12 H16 N4 O4; Mol wt: 280.2824

ACTION – An inhibitor of RNA-dependent RNA viral polymerase, particularly hepatitis C virus (HCV) NS5B polymerase, potentially useful for the treatment of HCV infection. Another exemplified nucleoside analogue is:



324683: C12 H16 N4 O4

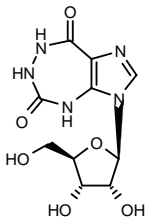
SOURCES – Isis Pharmaceuticals; Merck & Co.

REFERENCES

1. Carroll, S.S. et al. (Merck & Co., Inc.; Isis Pharmaceuticals, Inc.) *Nucleoside derivs. as inhibitors of RNA-dependent RNA viral polymerase.* WO 0257287.

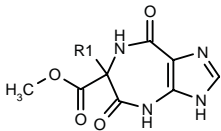
324851

3-(β-D-Ribofuranosyl)-3,4,5,6,7,8-hexahydroimidazo[4,5-e][1,2,4]triazepine-5,8-dione



C10 H13 N5 O6; Mol wt: 299.2417

ACTION – Ring-expanded nucleoside analogue for use in the treatment of bacterial, viral, fungal and protozoal infections including AIDS and hepatitis. This compound completely inhibited reverse transcriptase activity in Cas-Br-M murine leukemia virus at a concentration of 10.0 µg/ml. Other exemplified compounds are:



Compound	R1	Formula
324852	NH2	C ₈ H ₉ N ₅ O ₄
324853	OMe	C ₉ H ₁₀ N ₄ O ₅

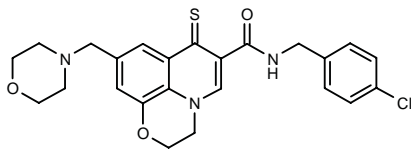
SOURCES – University of Maryland, Baltimore, MD (US); Nabi Biopharmaceuticals.

REFERENCES

1. Burns, B. and Hosmane, R. (Nabi Biopharmaceuticals Corp.;University of Maryland) *Ring-expanded nucleosides and nucleotides*. EP 1227103.

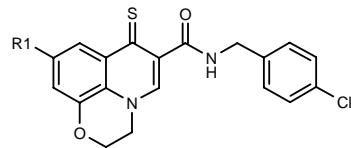
325858

N-(4-Chlorobenzyl)-9-(morpholin-4-ylmethyl)-7-thioxo-2,3-dihydro-7H-[1,4]oxazino[2,3,4-*ij*]quinoline-6-carboxamide



C24 H24 Cl N3 O3 S; Mol wt: 469.9906

ACTION – Viral DNA polymerase inhibitor (IC₅₀ = 0.06 µM for inhibition of human cytomegalovirus DNA polymerase), potentially useful for the treatment of infections caused by herpesviruses including cytomegalovirus, herpes simplex virus, varicella-zoster virus and Epstein-Barr virus. Other specifically claimed thioxazinoquinolones are:



Compound	R1	Formula
325860	ethynyl-CH2OH	C ₂₂ H ₁₇ ClN ₂ O ₃ S
325861	(CH2)3OH	C ₂₂ H ₂₁ ClN ₂ O ₃ S
325862	Pr	C ₂₂ H ₂₁ ClN ₂ O ₂ S

SOURCE – Pharmacia.

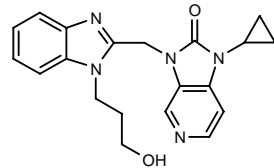
REFERENCES

1. Thorarensen, A. (Pharmacia Corp.) *Thioxazinoquinolones useful for the treatment of viral infections*. WO 0264145.

BMS-433771

325266

1-Cyclopropyl-3-[1-(3-hydroxypropyl)-1*H*-benzimidazol-2-ylmethyl]-2,3-dihydro-1*H*-imidazo[4,5-*c*]pyridin-2-one



C20 H21 N5 O2; Mol wt: 363.4189

ACTION – Antiviral agent active against respiratory syncytial virus (RSV; EC₅₀ = 0.009-0.05 µM) that blocks viral entry into cells via a direct interaction with F protein and inhibition of virus–cell fusion. Compound exhibited good oral bioavailability in mice, rats, dogs, and monkeys (32, 13, 72 and 42%, respectively). Following oral administration, it significantly reduced viral lung titers in mouse and cotton rat models of RSV infection.

SOURCE – Bristol-Myers Squibb.

REFERENCES

1. Yu, K.-L. et al. (Bristol-Myers Squibb Co.) *Imidazopyridine and imidazopyrimidine antiviral agents*. US 2002016309, US 6489338, WO 0195910.

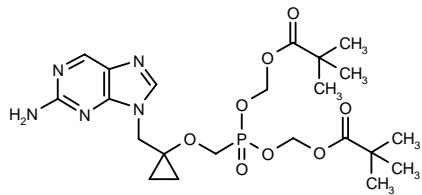
2. Cianci, C. et al. *Discovery of a new class of orally active respiratory syncytial virus inhibitors*. 42nd Intersci Conf Antimicrob Agents Chemother (Sept 27-30, San Diego) 2002, Abst F-1705.

LB-80380^{1,4,6-8}

325503

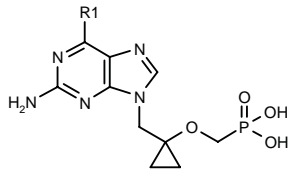
Bis(2,2-dimethylpropionic acid) 1-(2-amino-9*H*-purin-9-yl-methyl)cyclopropoxymethylphosphorylbis(oxyethylene) diester

1-(2-Amino-9*H*-purin-9-ylmethyl)cyclopropoxymethyl-phosphonic acid bis(pivaloyloxymethyl) diester



C22 H34 N5 O8 P; Mol wt: 527.5116

ACTION – Orally active double prodrug of **LB-80317**, a phosphonate nucleotide with potent and selective activity against both wild-type and lamivudine-resistant hepatitis B virus (HBV; EC₅₀ = 0.5 μM in HepG2 2.2.15 cells), but inactive against HIV or herpes simplex virus and with low cytotoxicity in human cell lines (CC₅₀ > 2.0 mM). The prodrug is rapidly converted to an intermediate metabolite, **LB-80331**, in peripheral blood, which is further metabolized to the parent compound LB-80317 intracellularly. Unlike the parent drug, the prodrug exhibited good oral bioavailability in rats, dogs and monkeys (25, 64 and 15%, respectively); the C_{max} and AUC values exceeded those of the estimated EC₅₀. The prodrug was effective in a transgenic mouse model of HBV infection at oral doses of 0.2-100 mg/kg/day for 10 days and in a woodchuck model at a dose of 5 mg/kg/day p.o. Extensive toxicological evaluation *in vitro* of LB-80317 and its prodrug indicated no mitochondrial toxicity and significantly less nephrotoxicity than adefovir. Although the prodrug was associated with moderate genotoxicity and mild toxicity in rats at higher doses, no evidence of any adverse drug-related effect was seen after 28-day treatment in dogs, and it was estimated to be over 10 times safer than other drugs used for HBV.



Compound	R1	Formula
LB-80317 [325502] ^{1,3-5,7}	OH	C ₁₀ H ₁₄ N ₅ O ₅ P
LB-80331 [325505] ^{1-4,8}	H	C ₁₀ H ₁₄ N ₅ O ₄ P

SOURCE – LG Chem Investment.

REFERENCES

1. Choi, J.-R. et al. (LG Chem Investment Ltd.) *Novel acyclic nucleoside phosphonate derivs., salts thereof and process for the preparation of the same*. WO 0257288.

2. Cho, Y.G. et al. *Cytotoxicities of LB80317 and its derivatives in Chinese hamster ovary cells expressing human renal organic anion transporter 1*. 42nd Intersci Conf Antimicrob Agents Chemother (Sept 27-30, San Diego) 2002, Abst F-1692.

3. Choi, J. et al. *Novel phosphonate nucleotides, LB80317 and its derivatives: Synthesis and anti-HBV activity*. 42nd Intersci Conf Antimicrob Agents Chemother (Sept 27-30, San Diego) 2002, Abst F-1688.

4. Choi, J. et al. *Synthesis and determination of oral bioavailability of prodrugs of a novel phosphonate nucleotide, LB80317*. 42nd Intersci Conf Antimicrob Agents Chemother (Sept 27-30, San Diego) 2002, Abst F-1689.

5. Kim, G.W. et al. *Evaluation of mitochondrial toxicities of new phosphonate derivatives*. 42nd Intersci Conf Antimicrob Agents Chemother (Sept 27-30, San Diego) 2002, Abst F-1691.

6. Kim, J. et al. *Discovery of a novel phosphonate nucleotide, LB80380: Synthesis, efficacy, safety and pharmacokinetics*. 42nd Intersci Conf Antimicrob Agents Chemother (Sept 27-30, San Diego) 2002, Abst F-1694.

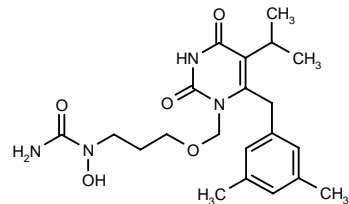
7. Kim, J. et al. *In vitro and in vivo activities of LB80380: A novel acyclic phosphonate nucleotide with potent anti-HBV activity*. 42nd Intersci Conf Antimicrob Agents Chemother (Sept 27-30, San Diego) 2002, Abst F-1690.

8. Kim, S.H. et al. *Pharmacokinetic and safety profiles of LB80380, a novel acyclic phosphonate nucleotide, as a new anti-HBV drug candidate*. 42nd Intersci Conf Antimicrob Agents Chemother (Sept 27-30, San Diego) 2002, Abst F-1693.

AIDS MEDICINES

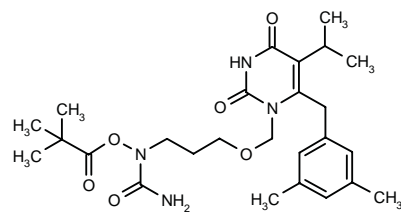
325271

6-(3,5-Dimethylbenzyl)-1-[3-(1-hydroxyureido)propoxy-methyl]-5-isopropyluracil



C21 H30 N4 O5; Mol wt: 418.4910

ACTION – HIV reverse transcriptase inhibitor proven to inhibit the replication of HIV-1 *in vitro* with an IC₅₀ of 2.3 nM and displaying low cytotoxicity against peripheral blood mononuclear cells (CC₅₀ = 260 μM; therapeutic index [TI] = 113,000). Potentially useful for the treatment of HIV infection. Another exemplified compound is:



325272: C26 H38 N4 O6

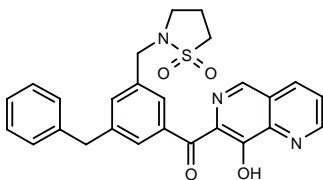
SOURCES – Université de Genève, Geneva (CH); Mayoly Spindler.

REFERENCES

1. Tronchet, J.M.J. (Université de Genève;Mayoly Spindler Laboratories) *Pyrimidine acyclonucleoside derivs., preparation method and use thereof*. WO 0260880.

325704

1-[3-Benzyl-5-(1,1-dioxoisothiazolidin-2-ylmethyl)phenyl]-1-(8-hydroxy-1,6-naphthyridin-7-yl)methanone



C26 H23 N3 O4 S; Mol wt: 473.5507

ACTION – HIV-1 integrase inhibitor ($IC_{50} = 10$ nM) able to inhibit HIV-1 replication in MT-4 cells ($IC_{95} = 0.39$ μ M); no cytotoxicity was seen up to 12.5 μ M. It exhibited a good pharmacokinetic profile in rats with an half-life of 9.7 h and moderate clearance after a dose of 2 mg/kg i.v.; plasma levels exceeding the IC_{95} value were maintained for 6 h after an oral dose of 10 mg/kg.

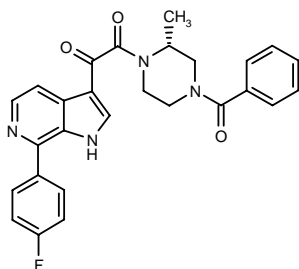
SOURCE – Merck & Co.

REFERENCES

1. Zhuang, L. et al. (Merck & Co., Inc.) *Aza- and polyaza-naphthalenyl ketones useful as HIV integrase inhibitors*. WO 0236734.
2. Zhuang, L. et al. *Design and synthesis of 8-hydroxy-1,6-naphthyridines as novel HIV-1 integrase inhibitors*. 42nd Intersci Conf Antimicrob Agents Chemother (Sept 27-30, San Diego) 2002, Abst LB-21.

326011

1-[4-Benzoyl-2(*R*)-methylpiperazin-1-yl]-2-[7-(4-fluorophenyl)-1*H*-pyrrolo[2,3-*c*]pyridin-3-yl]ethane-1,2-dione



C27 H23 F N4 O3; Mol wt: 470.5017

ACTION – Antiviral agent for use in the treatment of HIV infection, proven to inhibit HIV-1 infection in HeLa cells expressing CD4 and CCR5 receptors by 56% at 10 μ M.

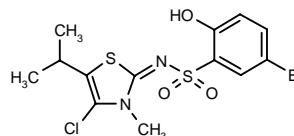
SOURCE – Bristol-Myers Squibb.

REFERENCES

1. Wang, T. et al. (Bristol-Myers Squibb Co.) *Compsn. and antiviral activity of subst. azaindoleoxoacetic piperazine derivs*. WO 0262423.

YM-215389**325267**

5-Bromo-*N*-(4-chloro-5-isopropyl-3-methylthiazol-2(3*H*)-ylidene)-2-hydroxybenzenesulfonamide



C13 H14 Br Cl N2 O3 S2; Mol wt: 425.7536

ACTION – Non-nucleoside HIV-1 reverse transcriptase inhibitor active against both wild-type and mutant (K103N, Y181C) enzymes ($IC_{50} = 0.0043$, 0.43 and 0.013 μ M, respectively) with potent anti-HIV-1 activity in MT-4 cells ($EC_{50} = 0.037$ μ M).

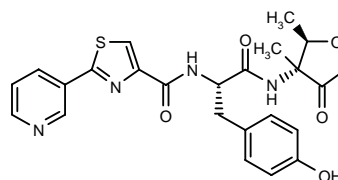
SOURCE – Yamanouchi.

REFERENCES

1. Yamamoto, O. et al. *Synthesis and structure-activity relationships of novel non-nucleoside HIV-1 reverse transcriptase inhibitors*. 42nd Intersci Conf Antimicrob Agents Chemother (Sept 27-30, San Diego) 2002, Abst F-1700.

TREATMENT OF PROTOZOAL DISEASES**324669**

*N*²-[2-(3-Pyridyl)thiazol-4-ylcarbonyl]-*N*¹-[2(*R*),3(*R*)-dimethyl-4-oxotetrahydrofuran-3-yl]-*L*-tyrosinamide



C24 H24 N4 O5 S; Mol wt: 480.5426

ACTION – A representative compound from a series of inhibitors of cruzipain, a cysteine protease of *Trypanosoma cruzi* parasites, giving a K_i of < 2 μ M against cruzipain and exhibiting selectivity over cathepsin S, cathepsin L and cathepsin K. By virtue of its activity, this compound has potential in the treatment of Chagas' disease.

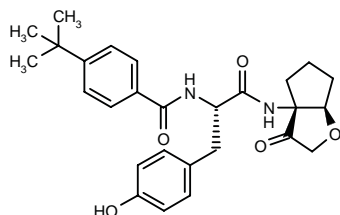
SOURCE – Amura.

REFERENCES

1. Quibell, M. (Incenta Ltd.) *Cyclic 2-carbonylaminoketones as inhibitors of cruzipain and other cysteine proteases*. WO 0257249.

324672

*N*²-(4-*tert*-Butylbenzoyl)-*N*¹-[(3*aR*,6*aR*)-3-oxo-perhydrocyclopenta[*b*]furan-3*a*-yl]-L-tyrosinamide



C27 H32 N2 O5; Mol wt: 464.5588

ACTION – A representative compound from a series of inhibitors of cruzipain, a cysteine protease of *Trypanosoma cruzi* parasites, giving a K_i of < 1 μ M against cruzipain and exhibiting selectivity over cathepsin S, cathepsin L and cathepsin K. By virtue of its activity, this compound has potential in the treatment of Chagas' disease.

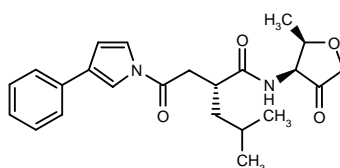
SOURCE – Amura.

REFERENCES

1. Quibell, M. and Ramjee, M.K. (Incenta Ltd.) *Inhibitors of cruzipain and other cysteine proteases*. WO 0257246.

324673

4-Methyl-*N*-[(2*R*,3*S*)-2-methyl-4-oxotetrahydrofuran-3-yl]-2(*R*)-[2-oxo-2-(3-phenyl-1*H*-pyrrol-1-yl)ethyl]pentanamide



C23 H28 N2 O4; Mol wt: 396.4842

ACTION – A representative compound from a series of inhibitors of cruzipain, a cysteine protease of *Trypanosoma cruzi* parasites, giving a K_i of < 5 μ M against cruzipain and exhibiting selectivity over cathepsin S, cathepsin L and cathepsin K. By virtue of its activity, this compound has potential in the treatment of Chagas' disease.

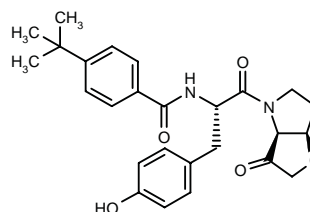
SOURCE – Amura.

REFERENCES

1. Quibell, M. (Incenta Ltd.) *Inhibitors of cruzipain and other cysteine proteases*. WO 0257248.

324674

4-*tert*-Butyl-*N*-[1(*S*)-(4-hydroxybenzyl)-2-oxo-2-[(3*aS*,6*aR*)-3-oxoperhydrofuro[3,2-*b*]pyrrol-4-yl]-ethyl]benzamide



C26 H30 N2 O5; Mol wt: 450.5320

ACTION – A representative compound from a series of inhibitors of cruzipain, a cysteine protease of *Trypanosoma cruzi* parasites, giving a K_i of 0.2 μ M against cruzipain and exhibiting selectivity over cathepsin S, cathepsin L and cathepsin K. By virtue of its activity, this compound may have potential in the treatment of Chagas' disease.

SOURCE – Amura.

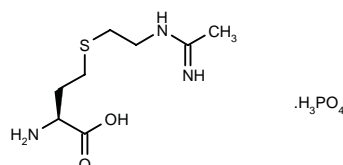
REFERENCES

1. Quibell, M. (Incenta Ltd.) *Inhibitors of cruzipain and other cysteine proteases*. WO 0257270.

TREATMENT OF MUSCULOSKELETAL AND CONNECTIVE TISSUE DISEASES**ANTIARTHRITIC DRUGS****323253**

2(*S*)-Amino-4-[2-(1-iminoethylamino)ethylsulfanyl]butyric acid phosphate

S-[2-(1-Iminoethylamino)ethyl]-L-homocysteine phosphate



C8 H17 N3 O2 S . H3 P O4; Mol wt: 317.3010

ACTION – A nonhygroscopic phosphate salt of the L-homocysteine derivative GW-274150⁺ with the ability to inhibit inducible nitric oxide synthase (iNOS). Potentially useful for the treatment of arthritis, asthma, rhinitis, ileus, migraine, pain and irritable bowel syndrome.

SOURCE – GlaxoSmithKline.

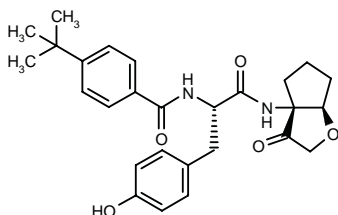
REFERENCES

1. Box, D. et al. (GlaxoSmithKline plc) *Nitric oxide synthase inhibitor phosphate salt*. WO 0250021.

⁺Drug Data Rep 2000, 022(08): 0702.

324672

*N*²-(4-*tert*-Butylbenzoyl)-*N*¹-[(3*aR*,6*aR*)-3-oxo-perhydrocyclopenta[*b*]furan-3*a*-yl]-L-tyrosinamide



C27 H32 N2 O5; Mol wt: 464.5588

ACTION – A representative compound from a series of inhibitors of cruzipain, a cysteine protease of *Trypanosoma cruzi* parasites, giving a K_i of < 1 μ M against cruzipain and exhibiting selectivity over cathepsin S, cathepsin L and cathepsin K. By virtue of its activity, this compound has potential in the treatment of Chagas' disease.

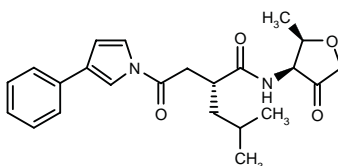
SOURCE – Amura.

REFERENCES

1. Quibell, M. and Ramjee, M.K. (Incenta Ltd.) *Inhibitors of cruzipain and other cysteine proteases*. WO 0257246.

324673

4-Methyl-*N*-[(2*R*,3*S*)-2-methyl-4-oxotetrahydrofuran-3-yl]-2(*R*)-[2-oxo-2-(3-phenyl-1*H*-pyrrol-1-yl)ethyl]pentanamide



C23 H28 N2 O4; Mol wt: 396.4842

ACTION – A representative compound from a series of inhibitors of cruzipain, a cysteine protease of *Trypanosoma cruzi* parasites, giving a K_i of < 5 μ M against cruzipain and exhibiting selectivity over cathepsin S, cathepsin L and cathepsin K. By virtue of its activity, this compound has potential in the treatment of Chagas' disease.

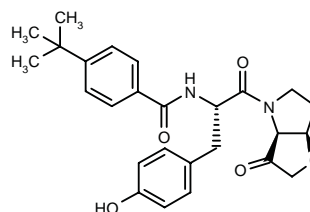
SOURCE – Amura.

REFERENCES

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324674

4-*tert*-Butyl-*N*-[1(*S*)-(4-hydroxybenzyl)-2-oxo-2-[(3*aS*,6*aR*)-3-oxoperhydrofuro[3,2-*b*]pyrrol-4-yl]-ethyl]benzamide



C26 H30 N2 O5; Mol wt: 450.5320

ACTION – A representative compound from a series of inhibitors of cruzipain, a cysteine protease of *Trypanosoma cruzi* parasites, giving a K_i of 0.2 μ M against cruzipain and exhibiting selectivity over cathepsin S, cathepsin L and cathepsin K. By virtue of its activity, this compound may have potential in the treatment of Chagas' disease.

SOURCE – Amura.

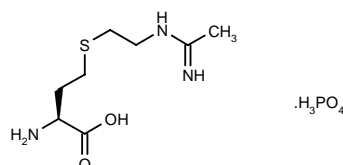
REFERENCES

1. Quibell, M. (Incenta Ltd.) *Inhibitors of cruzipain and other cysteine proteases*. WO 0257270.

TREATMENT OF MUSCULOSKELETAL AND CONNECTIVE TISSUE DISEASES**ANTIARTHRITIC DRUGS****323253**

2(*S*)-Amino-4-[2-(1-iminoethylamino)ethylsulfanyl]butyric acid phosphate

S-[2-(1-Iminoethylamino)ethyl]-L-homocysteine phosphate



C8 H17 N3 O2 S . H3 P O4; Mol wt: 317.3010

ACTION – A nonhygroscopic phosphate salt of the L-homocysteine derivative GW-274150⁺ with the ability to inhibit inducible nitric oxide synthase (iNOS). Potentially useful for the treatment of arthritis, asthma, rhinitis, ileus, migraine, pain and irritable bowel syndrome.

SOURCE – GlaxoSmithKline.

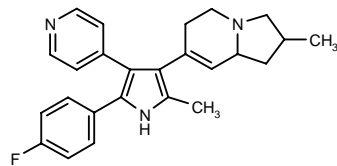
REFERENCES

1. Box, D. et al. (GlaxoSmithKline plc) *Nitric oxide synthase inhibitor phosphate salt*. WO 0250021.

⁺Drug Data Rep 2000, 022(08): 0702.

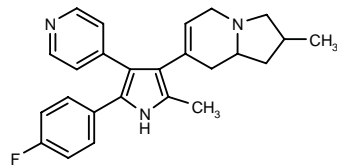
325171

(±)-7-[5-(4-Fluorophenyl)-2-methyl-4-(4-pyridyl)-1*H*-pyrrol-3-yl]-2-methyl-1,2,3,5,6,8a-hexahydroindolizine



C25 H26 F N3; Mol wt: 387.4994

ACTION – Agent with TNF-α and/or IL-1β production-inhibitory activity shown to inhibit the lipopolysaccharide-stimulated production of IL-1β in human peripheral blood cells by 98.03% at 1 μM. Potentially useful for the treatment of pain and inflammatory conditions including chronic rheumatoid arthritis, osteoarthritis, allergic diseases, sepsis, psoriasis, osteoporosis, ulcerative colitis, diabetes, hepatitis and arteriosclerosis. Another exemplified substituted pyrrole derivative is:



325172: C25 H26 F N3

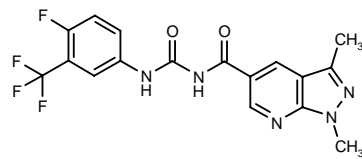
SOURCE – Sankyo.

REFERENCES

1. Kimura, T. et al. (Sankyo Co., Ltd.) 4- Or 5-substd. pyrrole derivs. JP 2002284780, WO 0257255.

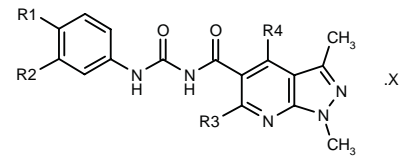
325532

N-(1,3-Dimethyl-1*H*-pyrazolo[3,4-*b*]pyridin-5-ylcarbonyl)-*N*'-[4-fluoro-3-(trifluoromethyl)phenyl]urea



C17 H13 F4 N5 O2; Mol wt: 395.3147

ACTION – Monocyte chemoattractant protein-1 (MCP-1) inhibitor found to inhibit MCP-1-induced chemotaxis in THP-1 cells with an IC₅₀ of 12.5 μM. It was also found to be active *in vivo* in several animal models including thioglycollate-induced inflammation and anti-Thy-1 antibody-induced nephritis in mice, the apolipoprotein E (apo E)-deficient mouse model of atherosclerosis and a rat model of restenosis. Potentially useful for the treatment of disorders associated with aberrant lymphocyte or monocyte accumulation such as asthma, atherosclerosis, glomerulonephritis, pancreatitis, restenosis, rheumatoid arthritis, diabetic nephropathy, pulmonary fibrosis, inflammatory bowel disease, Crohn's disease and transplant rejection. Other exemplified compounds are:



Compound	R1	R2	R3	R4	X	Formula
325534	F	CF3	H	4-Me-1-Piz	HCl	C ₂₂ H ₂₃ F ₄ N ₇ O ₂ .HCl
325537	H	i-PrO	N(Me)CH2-CH2N(Me)2	H		C ₂₄ H ₃₃ N ₇ O ₃
325538	4-morpholinyl-CO	Cl	H	H		C ₂₁ H ₂₁ ClN ₆ O ₄
325539	4-Me-1-Piz-CO	Cl	H	H		C ₂₂ H ₂₄ ClN ₇ O ₃

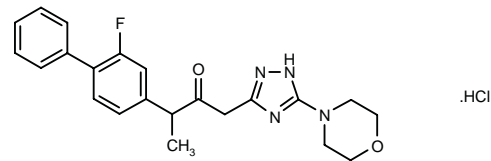
SOURCES – Sanwa; Telik.

REFERENCES

1. Laborde, E. et al. (Telik, Inc.;Sanwa Kagaku Kenkyusho Co., Ltd.) Antagonists of MCP-1 function and methods of use thereof. WO 0260900.

325663

3-(2-Fluorobiphenyl-4-yl)-1-[5-(4-morpholinyl)-1*H*-1,2,4-triazol-3-yl]butan-2-one hydrochloride



C22 H23 F N4 O2 . HCl; Mol wt: 430.9086

ACTION – A representative compound from a series of 5-membered heteroaryl derivatives for use in the treatment of autoimmune and inflammatory diseases. It demonstrated *in vivo* activity in the rat adjuvant-induced arthritis model following oral administration at a dose of 50 mg/kg for 5 days.

SOURCE – Sumitomo Pharmaceuticals.

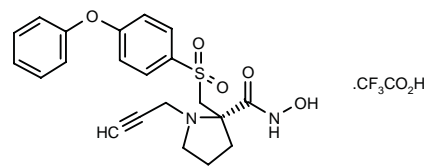
REFERENCES

1. Nakatsuka, M. et al. (Sumitomo Pharmaceuticals Co., Ltd.) 5-Membered heteroaromatic cyclic cpds. JP 2002212169.

325749

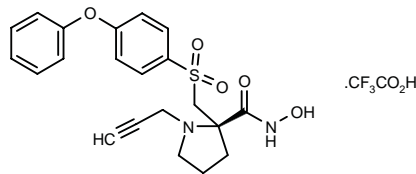
N-Hydroxy-2-(4-phenoxyphenylsulfonylmethyl)-1-(2-propynyl)-*D*-prolinamide trifluoroacetate

2(*R*)-(4-Phenoxyphenylsulfonylmethyl)-1-(2-propynyl)-pyrrolidine-2-carbohydroxamic acid trifluoroacetate



C21 H22 N2 O5 S . C2 H F3 O2; Mol wt: 528.5017

ACTION – Agent with the ability to inhibit matrix metallo-proteinases (MMPs), in particular MMP-2 (gelatinase A) and/or MMP-13 (collagenase 3), while having little or no activity against MMP-1 (interstitial collagenase). Potentially useful for the treatment of rheumatoid arthritis, osteoarthritis, septic arthritis, corneal, epidermal and gastric ulceration, cancer, periodontal disease, proteinuria, multiple sclerosis, Alzheimer’s disease and coronary thrombosis. Another specifically claimed compound is:



325750: C21 H22 N2 O5 S . C2 H F3 O2

SOURCE – Pharmacia.

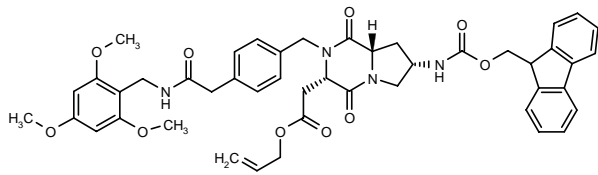
REFERENCES

1. Becker, D.P. et al. (Pharmacia Corp.) *Aromatic sulfonyl α-cycloamino hydroxamates and their use as MMP inhibitors*. WO 0262756.

325753

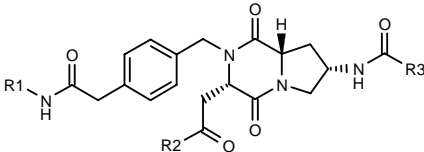
2-[(3*S*,7*S*,8*aS*)-7-(9*H*-Fluoren-9-ylmethoxycarbonylamino)-1,4-dioxo-2-[4-[*N*-(2,4,6-trimethoxybenzyl)carbamoylmethyl]benzyl]perhydropyrrolo[1,2-*a*]pyrazin-3-yl]acetic acid allyl ester

N-[(3*S*,7*S*,8*aS*)-3-[2-(Allyloxy)-2-oxoethyl]-1,4-dioxo-2-[4-[*N*-(2,4,6-trimethoxybenzyl)carbamoylmethyl]benzyl]perhydropyrrolo[1,2-*a*]pyrazin-7-yl]carbamic acid 9*H*-fluoren-9-ylmethyl ester



C46 H48 N4 O10; Mol wt: 816.9032

ACTION – Inhibitor of TNF-α-mediated processes such as the TNF-α-stimulated expression of NF-κB in A549 cells (IC₅₀ = 4 μM). Potentially useful for the treatment of disorders associated with elevated NF-κB, IL-8 or GROα levels, and CXCR1 and CXCR2 activity. Such disorders include rheumatoid arthritis, inflammatory bowel disease, psoriasis, atherosclerosis, asthma, reperfusion injury, ischemia, sepsis, transplant rejection, adult respiratory distress syndrome, multiple sclerosis, AIDS, bacterial meningitis, allergic inflammation of the respiratory tract, etc. Other exemplified diketopiperazines are:



Compound	R1	R2	R3	Formula
325754	2,4,6-(MeO)3-Ph-CH2	OH	9-fluorenyl-CH2O	C ₄₃ H ₄₄ N ₄ O ₁₀
325755	2,4,6-(MeO)3-Ph-CH2	OMe	3-quinolyl	C ₃₉ H ₄₁ N ₅ O ₉
325756	H	N(C6H13)(C5H11)	3-quinolyl	C ₃₉ H ₅₀ N ₆ O ₅

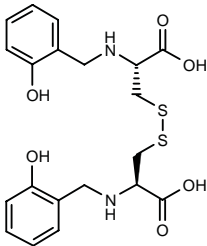
SOURCE – Celltech Group.

REFERENCES

1. Howbert, J.J. and Tabone, J.C. (Celltech Group plc) *Pharmaceutical uses and synthesis of diketopiperazines*. WO 0262797.

326247

N,N'-Bis(2-hydroxybenzyl)-L-cystine



C20 H24 N2 O6 S2; Mol wt: 452.5496

ACTION – A representative compound from a series of cystine derivatives with the ability to inhibit the activation of inflammatory factors. Title compound inhibited UV light-induced NF-κB activation in human epidermal cells by 41, 86 and > 100%, respectively, at 0.1, 0.5 and 1.0 mM. Potentially useful for the treatment of a broad range of inflammatory disorders including pain, reperfusion injury, septic shock, pneumonia, bronchitis, pancreatitis, meningitis, encephalitis, ulcerative colitis, inflammatory bowel disease, dermatitis, nephritis, arthritis, acne, alopecia, multiple sclerosis, transplant rejection, adult respiratory distress syndrome, diabetes, asthma, psoriasis and Alzheimer’s disease, among others.

SOURCE – Ajinomoto.

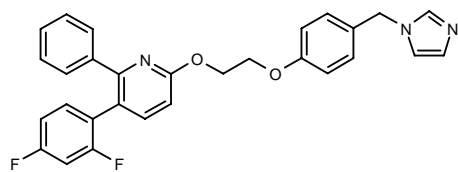
REFERENCES

1. Nakano, T. et al. (Ajinomoto Co., Inc.) *Novel cystine derivs. and inhibitors for the activation of inflammatory factors*. JP 2002226457, WO 0262751.

PPA-250

326842

3-(2,4-Difluorophenyl)-6-[2-[4-(1*H*-imidazol-1-ylmethyl)-phenoxy]ethoxy]-2-phenylpyridine



C29 H23 F2 N3 O2; Mol wt: 483.5157

ACTION – Antiinflammatory agent that inhibits nitric oxide (NO) production in murine macrophage RAW264.7 cells costimulated with lipopolysaccharide (LPS) and interferon gamma (IC₅₀ = 82 nM) via a mechanism that involves prevention of the dimerization of inducible NO (iNO). In LPS-treated mice, compound at a dose of 10 mg/kg p.o. and above significantly and dose-dependently reduced serum nitrite/nitrate levels. In mouse models of chronic inflammation such as collagen-induced arthritis and adjuvant-induced arthritis, oral doses of 3-30 mg/kg/day significantly and dose-dependently suppressed paw and joint inflammation, as well as the development of destructive polyarthritis. No systemic toxicity was seen at doses up to 100 mg/kg/day.

SOURCE – SSP.

REFERENCES

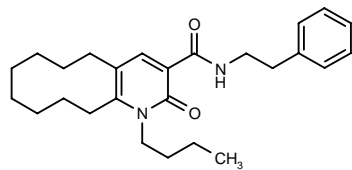
1. Konno, F. et al. (SSP Co., Ltd.) *Imidazole derivs. or salts thereof and drugs containing the derivs. or the salts.* WO 0200648.

2. Ohtsuka, M. et al. *PPA250 [3-(2,4-difluorophenyl)-6-[2-[4-(1*H*-imidazol-1-ylmethyl)phenoxy]ethoxy]-2-phenylpyridine], a novel orally effective inhibitor of the dimerization of inducible nitric-oxide synthase, exhibits an anti-inflammatory effect in animal models of chronic arthritis.* J Pharmacol Exp Ther 2002, 303(1): 52.

IMMUNOMODULATING AGENTS

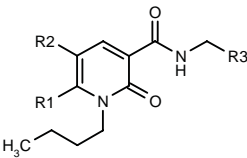
324174

1-Butyl-2-oxo-*N*-(2-phenylethyl)-1,2,5,6,7,8,9,10,11,12-decahydrocyclodeca[*b*]pyridine-3-carboxamide



C26 H36 N2 O2; Mol wt: 408.5824

ACTION – Agent with affinity for cannabinoid CB₂ receptors displaying K_i values of 4 and > 5000 nM for inhibition of [³H]-CP-55940 binding to human CB₂ and CB₁ receptors, respectively. Compound exhibited CB₂-agonist activity, as demonstrated by its ability to inhibit forskolin-stimulated cAMP production in CB₂-transfected CHO cells (IC₅₀ = 1.3 nM). Potentially useful as an antiinflammatory, antiallergic, analgesic and immunosuppressive agent. Other exemplified pyridone derivatives are:



Compound	R1	R2	R3	Formula
324175	Me	I	CH2Ph	C ₁₉ H ₂₃ N ₂ O ₂
324176	-(CH2)4-		Ph	C ₂₁ H ₂₆ N ₂ O ₂
324177	-(CH2)5-		Ph	C ₂₂ H ₂₈ N ₂ O ₂
324178	-(CH2)5-		CH2Ph	C ₂₃ H ₃₀ N ₂ O ₂
324179	-(CH2)5-		4-F-PhCH2	C ₂₃ H ₂₉ FN ₂ O ₂
324181	-(CH2)8-		Ph	C ₂₅ H ₃₄ N ₂ O ₂
324182	-(CH2)6-		Ph	C ₂₃ H ₃₀ N ₂ O ₂
324183	-(CH2)6-		CH2Ph	C ₂₄ H ₃₂ N ₂ O ₂
324184	-(CH2)6-		4-NH2-PhCH2	C ₂₄ H ₃₃ N ₃ O ₂

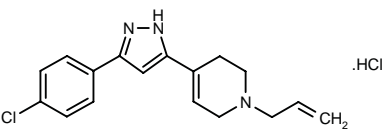
SOURCE – Shionogi.

REFERENCES

1. Tada, Y. et al. (Shionogi & Co. Ltd.) *Pyridone deriv. having affinity for cannabinoid 2-type receptor.* WO 0253543.

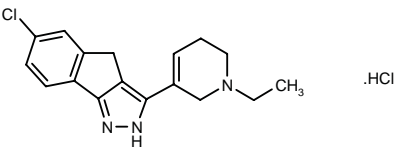
325235

1-Allyl-4-[3-(4-chlorophenyl)-1*H*-pyrazol-5-yl]-1,2,3,6-tetrahydropyridine hydrochloride



C17 H18 Cl N3 . HCl; Mol wt: 336.2641

ACTION – Immunosuppressant that inhibited the immune response induced by enterococcal enterotoxin B in mouse spleen cells with an IC₅₀ of 7.7 μM. *In vivo*, this compound inhibited the enlargement of lymph nodes of staphylococcal enterotoxin B-challenged mice by 46.2% at 50 mg/kg/day p.o. for 3 days. Potentially useful for the treatment of autoimmune and allergic diseases, particularly ulcerative colitis, chronic rheumatoid arthritis and multiple sclerosis. Another exemplified pyrazole derivative is:

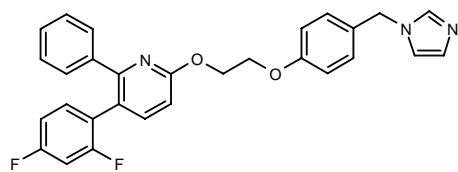


325237: C17 H18 Cl N3 . HCl

PPA-250

326842

3-(2,4-Difluorophenyl)-6-[2-[4-(1*H*-imidazol-1-ylmethyl)-phenoxy]ethoxy]-2-phenylpyridine



C29 H23 F2 N3 O2; Mol wt: 483.5157

ACTION – Antiinflammatory agent that inhibits nitric oxide (NO) production in murine macrophage RAW264.7 cells costimulated with lipopolysaccharide (LPS) and interferon gamma (IC₅₀ = 82 nM) via a mechanism that involves prevention of the dimerization of inducible NO (iNO). In LPS-treated mice, compound at a dose of 10 mg/kg p.o. and above significantly and dose-dependently reduced serum nitrite/nitrate levels. In mouse models of chronic inflammation such as collagen-induced arthritis and adjuvant-induced arthritis, oral doses of 3-30 mg/kg/day significantly and dose-dependently suppressed paw and joint inflammation, as well as the development of destructive polyarthritis. No systemic toxicity was seen at doses up to 100 mg/kg/day.

SOURCE – SSP.

REFERENCES

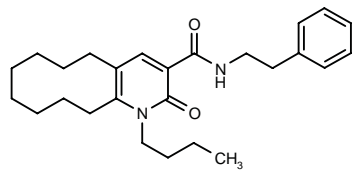
1. Konno, F. et al. (SSP Co., Ltd.) *Imidazole derivs. or salts thereof and drugs containing the derivs. or the salts.* WO 0200648.

2. Ohtsuka, M. et al. *PPA250 [3-(2,4-difluorophenyl)-6-[2-[4-(1*H*-imidazol-1-ylmethyl)phenoxy]ethoxy]-2-phenylpyridine], a novel orally effective inhibitor of the dimerization of inducible nitric-oxide synthase, exhibits an anti-inflammatory effect in animal models of chronic arthritis.* J Pharmacol Exp Ther 2002, 303(1): 52.

IMMUNOMODULATING AGENTS

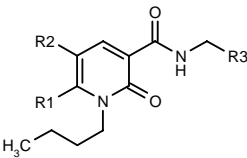
324174

1-Butyl-2-oxo-*N*-(2-phenylethyl)-1,2,5,6,7,8,9,10,11,12-decahydrocyclodeca[*b*]pyridine-3-carboxamide



C26 H36 N2 O2; Mol wt: 408.5824

ACTION – Agent with affinity for cannabinoid CB₂ receptors displaying K_i values of 4 and > 5000 nM for inhibition of [³H]-CP-55940 binding to human CB₂ and CB₁ receptors, respectively. Compound exhibited CB₂-agonist activity, as demonstrated by its ability to inhibit forskolin-stimulated cAMP production in CB₂-transfected CHO cells (IC₅₀ = 1.3 nM). Potentially useful as an antiinflammatory, antiallergic, analgesic and immunosuppressive agent. Other exemplified pyridone derivatives are:



Compound	R1	R2	R3	Formula
324175	Me	I	CH2Ph	C ₁₉ H ₂₃ N ₂ O ₂
324176	-(CH2)4-		Ph	C ₂₁ H ₂₆ N ₂ O ₂
324177	-(CH2)5-		Ph	C ₂₂ H ₂₈ N ₂ O ₂
324178	-(CH2)5-		CH2Ph	C ₂₃ H ₃₀ N ₂ O ₂
324179	-(CH2)5-		4-F-PhCH2	C ₂₃ H ₂₉ FN ₂ O ₂
324181	-(CH2)8-		Ph	C ₂₅ H ₃₄ N ₂ O ₂
324182	-(CH2)6-		Ph	C ₂₃ H ₃₀ N ₂ O ₂
324183	-(CH2)6-		CH2Ph	C ₂₄ H ₃₂ N ₂ O ₂
324184	-(CH2)6-		4-NH2-PhCH2	C ₂₄ H ₃₃ N ₃ O ₂

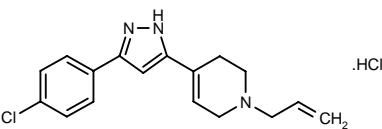
SOURCE – Shionogi.

REFERENCES

1. Tada, Y. et al. (Shionogi & Co. Ltd.) *Pyridone deriv. having affinity for cannabinoid 2-type receptor.* WO 0253543.

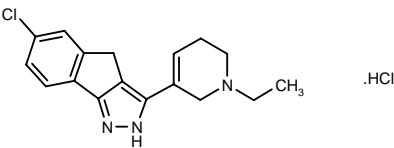
325235

1-Allyl-4-[3-(4-chlorophenyl)-1*H*-pyrazol-5-yl]-1,2,3,6-tetrahydropyridine hydrochloride



C17 H18 Cl N3 . HCl; Mol wt: 336.2641

ACTION – Immunosuppressant that inhibited the immune response induced by enterococcal enterotoxin B in mouse spleen cells with an IC₅₀ of 7.7 μM. *In vivo*, this compound inhibited the enlargement of lymph nodes of staphylococcal enterotoxin B-challenged mice by 46.2% at 50 mg/kg/day p.o. for 3 days. Potentially useful for the treatment of autoimmune and allergic diseases, particularly ulcerative colitis, chronic rheumatoid arthritis and multiple sclerosis. Another exemplified pyrazole derivative is:



325237: C17 H18 Cl N3 . HCl

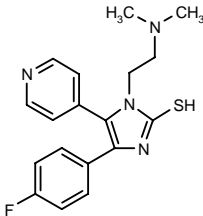
SOURCE – Sumitomo Pharmaceuticals.

REFERENCES

1. Nakatsuka, M. et al. (Sumitomo Pharmaceuticals Co., Ltd.) *Pyrazole derivs. and their medicinal use*. JP 2002193964.

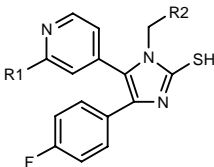
326365

1-[2-(Dimethylamino)ethyl]-4-(4-fluorophenyl)-5-(4-pyridyl)-1*H*-imidazole-2-thiol



C18 H19 F N4 S; Mol wt: 342.4401

ACTION – Agent with the ability to prevent cytokine release, potentially useful as an immunomodulatory agent. Compound was shown to inhibit the lipopoly-saccharide-stimulated production of TNF-α and IL-1β in *in vitro* assays. Other specifically claimed imidazole derivatives are:



Compound	R1	R2	Formula
326366	H	CH2CH2N(Me)2	C ₁₉ H ₂₁ FN ₄ S
326368	NHEt	H	C ₁₇ H ₁₇ FN ₄ S

SOURCE – Merckle.

REFERENCES

1. Laufer, S. et al. (Merckle GmbH) *2-Thio-substd. imidazole derivs. and the use thereof in the pharmaceutical industry*. DE 10107683, WO 0266458.

CHIMERIVAX™-WN

292956

West Nile (WN) encephalitis vaccine produced using the ChimeriVax technology consisting of a chimeric live virus containing the capsid and nonstructural genes of the yellow fever (YF) 17D virus and the envelope genes (prME) of West Nile NY99 virus

ChimeriVax™-West Nile

ACTION – Live, attenuated West Nile virus vaccine consisting of a chimeric live virus containing the capsid and nonstructural genes of yellow fever (YF) and the envelope genes (prME) of West Nile (WN NY99) virus. It was well tolerated in mice and monkeys, induced high levels of neutralizing antibodies and protected against challenge with wild-type West Nile virus.

SOURCE – Acambis.

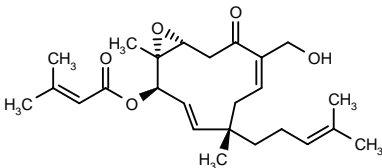
REFERENCES

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2. Arroyo, J. et al. *Yellow fever vector live-virus vaccines: West Nile virus vaccine development*. Trends Mol Med 2001, 7(8): 350.
3. *Peptide Therapeutics awarded SBIR grant for West Nile vaccine*. DailyDrugNews.com (Daily Essentials) 2000, Aug 4.

EPOXYVIBSANIN B

325549

3-Methyl-2-butenic acid (1*R*,2*R*,5*S*,11*R*)-8-(hydroxy-methyl)-1,5-dimethyl-5-(4-methyl-3-pentenyl)-9-oxo-12-oxabicyclo[9.1.0]dodeca-3,7-dien-2-yl ester



C25 H36 O5; Mol wt: 416.5544

ACTION – IL-12 production inhibitor isolated from the plant *Caprifoliaceae vibrunum* Awabuki. It inhibited the interferon gamma- and lipopolysaccharide-stimulated production of IL-12 in peripheral blood mononuclear cells (PBMCs) by 90% at a concentration of 1 μg/ml. In cytotoxicity assays, it showed CC₅₀ values of 5 and 10 μM, respectively, against PBMCs and THP-1 cells, being less cytotoxic than dexamethasone. Potentially useful for the treatment of autoimmune diseases.

SOURCE – Shionogi BioResearch.

REFERENCES

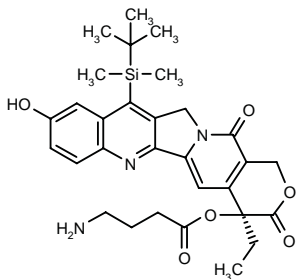
1. Ono, M. et al. (Shionogi BioResearch Corp.) *Epoxyvibsanin B*. US 6462078, WO 0260922.

ONCOLYTIC DRUGS

DNA-INTERCALATING DRUGS

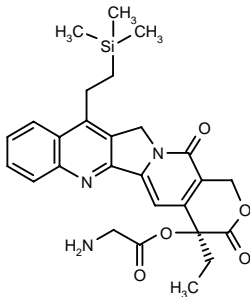
325803

4-Aminobutyric acid 7-(*tert*-butyldimethylsilyl)-10-hydroxy-camptothecin-20(*S*)-*O*-yl ester



C30 H37 N3 O6 Si; Mol wt: 563.7233

ACTION – A prodrug of DB-67⁺, a known camptothecin derivative, with highly lipophilic properties. Potentially useful for the treatment of cancer and AIDS. Another exemplified compound is:



325804: C27 H31 N3 O5 Si

SOURCE – University of Kentucky, Lexington, KY (US).

REFERENCES

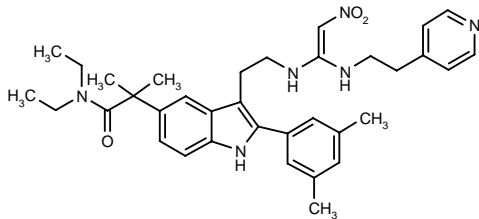
1. Bom, D.C. and Burke, T.G. (University of Kentucky) *Highly lipophilic camptothecin prodrugs, methods of preparation, and formulations thereof*. WO 0262340.

*Drug Data Rep 2001, 023(03): 0297.

HORMONAL AGENTS

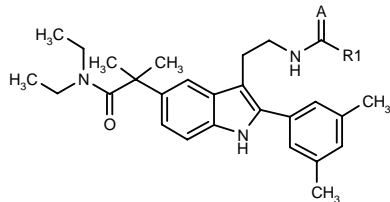
326295

2-[2-(3,5-Dimethylphenyl)-3-[2-[2-nitro-1-[2-(4-pyridyl)-ethylamino]vinylamino]ethyl]-1-*H*-indol-5-yl]-*N,N*-diethyl-2-methylpropionamide

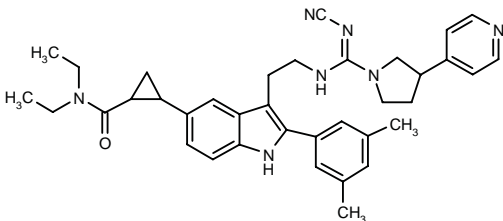


C35 H44 N6 O3; Mol wt: 596.7716

ACTION – Gonadotropin-releasing hormone (GnRH) antagonist expected to be useful for the treatment of sex hormone-dependent cancer, benign prostatic hyperplasia and uterine myoma. Other specifically claimed indole derivatives are:



Compound	R1	A	Formula
326296	4-Pyr-CH2CH2NH	N(CN)	C ₃₅ H ₄₃ N ₇ O
326297	2-Pyr-CH2CH2NH	N(CN)	C ₃₅ H ₄₃ N ₇ O
326298	1-imidazolyl-CH2CH2NH	N(CN)	C ₃₃ H ₄₂ N ₈ O
326308	NHCH2CH2Ph	O	C ₃₅ H ₄₄ N ₄ O ₂
326310	4-Pyr-CH2CH2NH	O	C ₃₄ H ₄₃ N ₅ O ₂
326311	4-Me-1-Piz-(CH2)3NH	N(CN)	C ₃₆ H ₅₂ N ₆ O
326312	2-Pip-CH2CH2NH	N(CN)	C ₃₅ H ₄₉ N ₇ O
326314	3-(4-Pyr)-1-pyrrolidiny	N(CN)	C ₃₇ H ₄₅ N ₇ O
326318	4-Pyr-CH2CH2N(Me)	N(CN)	C ₃₆ H ₄₅ N ₇ O
326319	3-(4-Pyr)-1-pyrrolidiny	C(NO2)	C ₃₇ H ₄₆ N ₆ O ₃
326331	3-(4-Pyr)-1-pyrrolidiny	O	C ₃₆ H ₄₅ N ₅ O ₂
326332	3-(4-Pyr)-1-pyrrolidiny	NH	C ₃₆ H ₄₆ N ₆ O



326333: C37 H43 N7 O

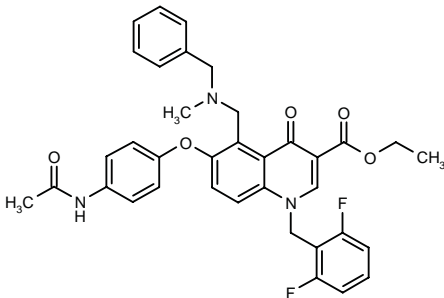
SOURCE – AstraZeneca.

REFERENCES

1. Wardleworth, M. et al. (AstraZeneca AB;AstraZeneca plc) *Indole derivs. and their use as GnRH antagonists*. WO 0266459.

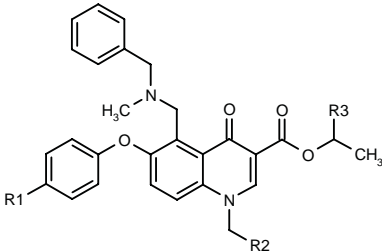
326301

6-(4-Acetamidophenoxy)-5-(*N*-benzyl-*N*-methylamino-methyl)-1-(2,6-difluorobenzyl)-4-oxo-1,4-dihydroquino-line-3-carboxylic acid ethyl ester

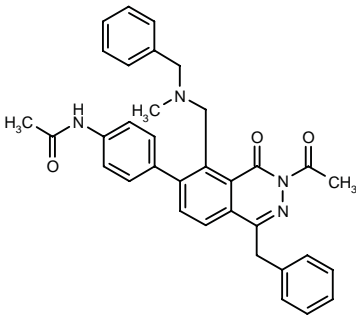


C36 H33 F2 N3 O5; Mol wt: 625.6687

ACTION – Gonadotropin-releasing hormone (GnRH) antagonist expected to be useful for the treatment of female infertility, male and female contraception and cancer. Other exemplified compounds are:



Compound	R1	R2	R3	Formula
326302	NHAc	2,6-(F)2-Ph	Me	C ₃₇ H ₃₅ F ₂ N ₃ O ₅
326303	i-PrCONH	2,6-(F)2-Ph	H	C ₃₈ H ₃₇ F ₂ N ₃ O ₅
326305	NHAc	2-CF3-Ph	H	C ₃₇ H ₃₄ F ₃ N ₃ O ₅
326306	CONHMe	2,6-(F)2-Ph	H	C ₃₈ H ₃₃ F ₂ N ₃ O ₅
326307	NHAc	1-Naph	H	C ₄₀ H ₃₇ N ₃ O ₅



326304: C34 H32 N4 O3

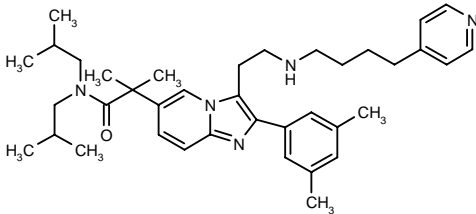
SOURCE – Schering AG.

REFERENCES

1. Strehlke, P. et al. (Schering AG) *Quinoline, isoquinoline and phthalazine derivs. as antagonists of the gonadotropin-releasing hormone*. WO 0266437.

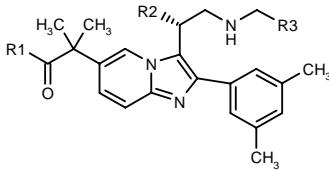
326345

2-[2-(3,5-Dimethylphenyl)-3-[2-[4-(4-pyridyl)butylamino]-ethyl]imidazo[1,2-*a*]pyridin-6-yl]-*N,N*-diisobutyl-2-methyl-propionamide

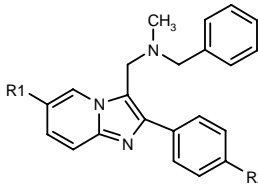


C38 H53 N5 O; Mol wt: 595.8707

ACTION – Gonadotropin-releasing hormone (GnRH) antagonist expected to be useful for the treatment of sex hormone-dependent cancer, benign prostatic hyperplasia and uterine myoma. Other specifically claimed compounds include the following:



Compound	R1	R2	R3	Formula
326348	7-azabicyclo[2.2.1]hept-7-yl	H	4-(3-Pyr)-Ph	C ₃₉ H ₄₃ N ₅ O
326349	7-azabicyclo[2.2.1]hept-7-yl	Me	3-Me-6-imidazo-[4,5-b]pyridinyl-CH2	C ₃₇ H ₄₅ N ₇ O
326350	N(Et)2	H	4-Pyr-(CH2)3	C ₃₄ H ₄₅ N ₅ O



Compound	R1	R2	Formula
326352	4-oxazolyl	OMe	C ₂₈ H ₂₄ N ₄ O ₂
326353	CO2Et	OMe	C ₂₈ H ₂₇ N ₃ O ₃
326355	i-PrCO	i-PrCONH	C ₃₀ H ₃₄ N ₄ O ₂
326357	i-PrOCO	i-PrCONH	C ₃₀ H ₃₄ N ₄ O ₃
326358	i-PrNHCO	NHCONHMe	C ₂₈ H ₃₂ N ₆ O ₂

SOURCE – AstraZeneca.

REFERENCES

1. Dossetter, A.G. et al. (AstraZeneca AB;AstraZeneca plc) *Compounds*. WO 0266477.

CANCER IMMUNOTHERAPY

DEXOSOME VACCINE (MELANOMA)

325648

Vaccine consisting of exosomes isolated from dendritic cells of cancer patients (dexosomes) loaded with the tumor-associated antigens known as MAGE peptides (MAGE-3.A1 and MAGE-3.DP04)

ACTION – Melanoma vaccine consisting of exosomes isolated from dendritic cells (dexosomes) of cancer patients loaded with tumor-associated MAGE-3 peptides, able to induce a T-cell response against tumor cells. Preliminary results of a phase I clinical trial in patients with advanced melanoma showed that escalating s.c. doses of vaccine were well tolerated, without evidence of serious toxicity. Currently in phase II clinical trials.

SOURCES – Anosys; Kirin Brewery.

REFERENCES

1. Escudier, B. et al. *Phase I trial of dexosome vaccine for patients with advanced melanoma: Final results.* Ann Oncol 2002, 13(Suppl. 5): Abst 580O.

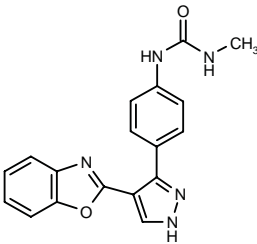
2. Escudier, B.J. et al. *Novel approach to immunotherapy of cancer: Phase I trial of dexosome vaccine for patients with advanced melanoma.* Proc Am Soc Clin Oncol 2002, 21(Part 2): Abst 1857.

3. Hsu, D.-H. et al. *A novel acellular approach to cancer immunotherapy: Dexosomes, from bench to bedside.* Proc Am Assoc Cancer Res 2002, 43: Abst 3362.

INHIBITORS OF SIGNAL TRANSDUCTION PATHWAYS

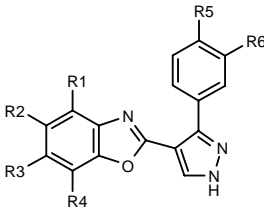
325764

N-[4-[4-(Benzoxazol-2-yl)-1H-pyrazol-3-yl]phenyl]-N'-methylurea

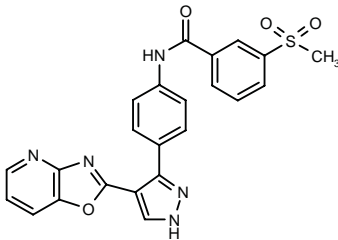


C18 H15 N5 O2; Mol wt: 333.3495

ACTION – Protein kinase inhibitor with potential in the treatment of cancer and other cell proliferative disorders, Alzheimer’s disease and other neurodegenerative disorders, viral infections and autoimmune diseases. Other exemplified compounds include the following:



Compound	R1	R2	R3	R4	R5	R6	Formula
325765	H	H	Me	H	H	NHCOPh	C ₂₄ H ₁₈ N ₄ O ₂
325768	H	H	Me	H	NHCOCOEt	H	C ₂₁ H ₁₈ N ₄ O ₃
325770	H	Me	H	H	1-Ph-5-Me-4-pyrazolyl-CONH	H	C ₂₈ H ₂₂ N ₆ O ₂
325771	H	Ph	H	H	5-(AcNH)-2-NO ₂ -PhCONH	H	C ₃₁ H ₂₂ N ₆ O ₅
325773	H	t-Bu	H	H	H	5-isoxazolyl-CONH	C ₂₄ H ₂₁ N ₅ O ₃
325774	Me	H	H	i-Pr	H	cyclobutyl-CONH	C ₂₅ H ₂₆ N ₄ O ₂



325772: C23 H17 N5 O4 S

SOURCE – Pharmacia.

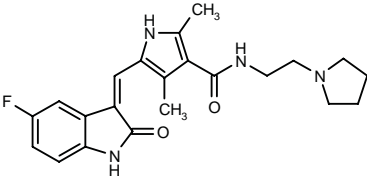
REFERENCES

1. Berta, D. et al. (Pharmacia Italia SpA) *Oxazolyl-pyrazole derivs. as kinase inhibitors.* WO 0262804.

SU-11654¹⁻⁴

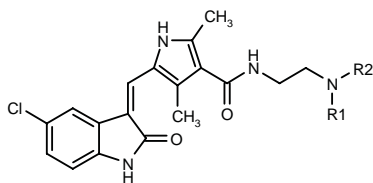
311900

(Z)-5-(5-Fluoro-2-oxo-2,3-dihydro-1H-indol-3-ylidenemethyl)-2,4-dimethyl-N-[2-(1-pyrrolidinyl)ethyl]-1H-pyrrole-3-carboxamide



C22 H25 F N4 O2; Mol wt: 396.4635

ACTION – Protein tyrosine kinase inhibitor active against vascular endothelial growth factor receptor (VEGFR), fibroblast growth factor receptor (FGFR), platelet-derived growth factor receptor (PDGFR) and Kit, a receptor tyrosine kinase encoded by the proto-oncogene *c-kit* that binds the ligand stem cell factor (SCF). In mast cell lines, compound (0.01-0.5 μM) inhibited both the phosphorylation of wild-type Kit and the autophosphorylation of two JM domain mutants. It also inhibited the growth of mast cell lines expressing these two Kit mutations and induced initial cell cycle arrest, followed by different degrees of apoptosis at different time points and concentrations. Cell death at 24 h was seen in another cell line expressing a catalytic domain mutation. Potentially useful as a broad-spectrum antitumor agent. Other related compounds are:



Compound	R1	R2	Formula
SU-11652 [325099] ¹⁻³	Et	Et	C ₂₂ H ₂₇ ClN ₄ O ₂
SU-11655 [325101] ¹⁻³	-(CH ₂) ₄ -		C ₂₂ H ₂₅ ClN ₄ O ₂

SOURCE – Sugen (Pharmacia).

REFERENCES

1. Lipson, K. and McMahon, G. (Sugen, Inc.) *Methods of modulating c-kit tyrosine protein kinase function with indolinone cpds*. WO 0145689.

2. Tang, P.C. et al. (Sugen, Inc.) *Pyrrole substd. 2-indolinone protein kinase inhibitors*. EP 1255752; WO 0160814.

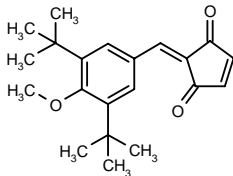
3. Liao, A.T. et al. *Inhibition of constitutively active forms of mutant kit by multitargeted indolinone tyrosine kinase inhibitors*. Blood 2002, 100(2): 585.

4. London, C.A. et al. *Inhibition of constitutively active forms of mutant kit utilizing an indolinone kinase inhibitor*. Blood 2001, 98(11, Part 1): Abst 2410.

TX-1925

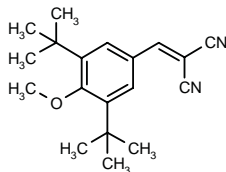
326496

2-(3,5-Di-*tert*-butyl-4-methoxybenzylidene)-4-cyclopentene-1,3-dione



C₂₁ H₂₆ O₃; Mol wt: 326.4334

ACTION – Protein tyrosine kinase inhibitor active against Src and eukaryotic elongation factor 2 (eEF2) kinases (IC₅₀ = 3.1 μM) with 10-fold selectivity over protein kinase A and C (PKA, PKC) and epidermal growth factor receptor (EGFR) kinase. It exhibited cytotoxic activity against human colon carcinoma HCT 116 and human hepatocellular carcinoma HepG2 cells (IC₅₀ = 89 and 6.36 μM, respectively) and lower mitochondrial toxicity compared to other compounds of this series. Another related compound is:



TX-1927 [326497]: C₁₉ H₂₄ N₂ O

SOURCES – National Institutes of Health, Bethesda, MD (US); National Institute of Infectious Diseases, Tokyo (JP); University of Tokushima, Tokushima (JP).

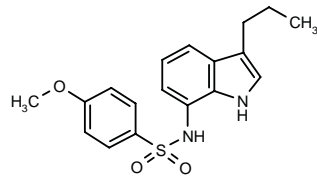
REFERENCES

1. Hori, H. et al. *TX-1123: An antitumor 2-hydroxyarylidene-4-cyclopentene-1,3-dione as a protein tyrosine kinase inhibitor having low mitochondrial toxicity*. Bioorg Med Chem 2002, 10(10): 3257.

ANGIOGENESIS INHIBITORS

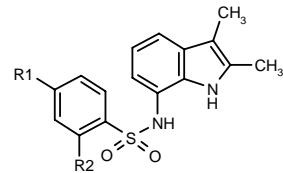
324407

4-Methoxy-*N*-(3-propyl-1*H*-indol-7-yl)benzenesulfonamide

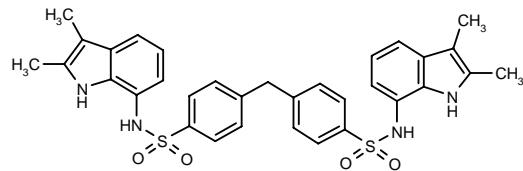


C₁₈ H₂₀ N₂ O₃ S; Mol wt: 344.4330

ACTION – Inhibitor of vascular endothelial growth factor (VEGF) production, as demonstrated in human fibroblasts (83.8% inhibition at 10 μM). Potentially useful for the treatment of disorders associated with neovascularization including cancer, arthritis and ocular disorders such as diabetic retinopathy, age-related macular degeneration, glaucoma and retinal vascular disease. Other exemplified indole derivatives are:



Compound	R1	R2	Formula
324408	OMe	NO ₂	C ₁₇ H ₁₇ N ₃ O ₅ S
324409	OMe	H	C ₁₇ H ₁₈ N ₂ O ₃ S
324410	NHAc	H	C ₁₈ H ₁₉ N ₃ O ₃ S



324411: C₃₃ H₃₂ N₄ O₄ S₂

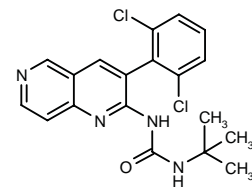
SOURCE – Mercian.

REFERENCES

1. Nagai, H. et al. (Mercian Corp.) *Indole derivs. having an inhibitory effect to expression of vascular endothelial cell growth factor and their use*. JP 2002167376.

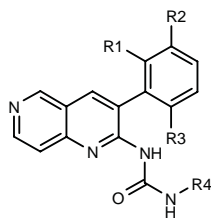
325506

N-*tert*-Butyl-*N*-[3-(2,6-dichlorophenyl)-1,6-naphthyridin-2-yl]urea



C₁₉ H₁₈ Cl₂ N₄ O; Mol wt: 389.2842

ACTION – Tie2 receptor tyrosine kinase inhibitor with antiangiogenic activity. Potentially useful for the treatment of chronic inflammatory or proliferative diseases. Other specifically claimed compounds are:



Compound	R1	R2	R3	R4	Formula
325507	F	H	Cl	t-Bu	C ₁₉ H ₁₈ ClFN ₄ O
325508	Cl	H	F	2-THP	C ₂₀ H ₁₈ ClFN ₄ O ₂
325509	H	Me	Me	t-Bu	C ₂₁ H ₂₄ N ₄ O
325510	H	Me	Me	Et	C ₁₉ H ₂₀ N ₄ O
325511	H	Me	Me	2-THP	C ₂₂ H ₂₄ N ₄ O ₂

SOURCE – GlaxoSmithKline.

REFERENCES

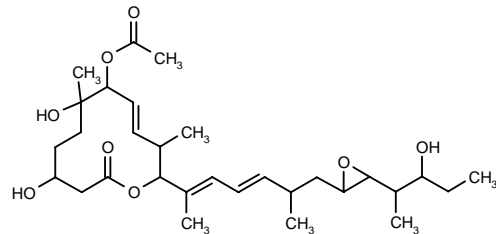
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MER-11107B

325950

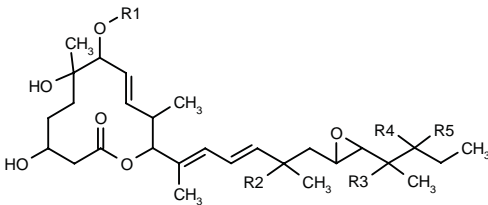
7-Acetoxy-11-(7,8-epoxy-10-hydroxy-1,5,9-trimethyl-1,3-dodecadienyl)-3,6-dihydroxy-6,10-dimethyl-8-undecenolide

7-Acetoxy-18,19-epoxy-3,6,21-trihydroxy-6,10,12,16,20-pentamethyl-8,12,14-tricosatrieno-11-lactone



C30 H48 O8; Mol wt: 536.7012

ACTION – Antiangiogenic compound isolated from cultures of *Streptomyces* sp. Mer-11107 (FERM -18144). Mer-11107B inhibited the production of vascular endothelial growth factor (VEGF) in various cancer cell lines with IC₅₀ values below 2.0 ng/ml. It also showed antiproliferative activity *in vitro* against human megakaryoblast Dami (IC₅₀ = 1.2 nM), human acute lymphoblastic leukemia MOLT-4 (IC₅₀ = 1.5 nM), human histiocytic lymphoma U-937 (IC₅₀ = 1.1 nM), human chronic myelogenous leukemia K-562 (IC₅₀ = 2.1 nM) and murine leukemia P388 cells (IC₅₀ = 2.0 nM). *In vivo*, Mer-11107B displayed antitumor activity against human breast cancer BSY-1 xenografts and colon cancer WiDr xenografts implanted s.c. into nude mice following i.v. administration at a dose of 10 mg/kg. Potentially useful for the treatment of cancer, hemangioma, disorders associated with retinal neovascularization, diabetic retinopathy, inflammatory disorders such as arthritis, psoriasis and delayed hypersensitivity reaction, and atherosclerosis. Other exemplified compounds from the same source are:



Compound	R1	R2	R3	R4	R5	Formula
Mer-11107C [325951]	Ac	H	H	-O-		C ₃₀ H ₄₆ O ₈
Mer-11107D [325952]	Ac	OH	H	OH	H	C ₃₀ H ₄₈ O ₉
Mer-11107E [325953]	Ac	H	OH	OH	H	C ₃₀ H ₄₈ O ₉
Mer-11107A [325954]	H	H	H	OH	H	C ₂₈ H ₄₆ O ₇

SOURCES – Eisai; Mercian.

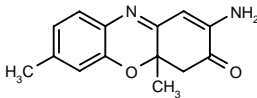
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OTHER ONCOLYTIC DRUGS

307064

2-Amino-4a,7-dimethyl-4,4a-dihydro-3H-phenoxazin-3-one



C14 H14 N2 O2; Mol wt: 242.2766

ACTION – Antineoplastic agent, a phenoxazine derivative found to inhibit the proliferation of several human leukemia cell lines including erythroleukemia K-562, myeloid leukemia HL-60 and lymphoblastic leukemia HAL-01 cells (IC₅₀ = 73, 81 and 93 μM, respectively), as well as human B- and T-cell-derived lymphoblastoid cell lines. It inhibited cell growth by a mechanism that involved apoptosis, cell cycle arrest and DNA synthesis inhibition. No toxicity was seen against normal bone marrow progenitors.

SOURCE – Tokyo Medical and Dental University, Tokyo (JP).

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1. Abe, A. et al. *Prevention of growth of human lung carcinoma cells and induction of apoptosis by a novel phenoxazinone, 2-amino-4,4a-dihydro-4a,7-dimethyl-3H-phenoxazine-3-one*. Anti-Cancer Drugs 2001, 12(4): 377.

2. Akazawa, M. et al. *Effects of novel phenoxazine compounds, 2-amino-4,4a-dihydro-4a,7-dimethyl-3H-phenoxazine-3-one and 3-amino-1,4a-dihydro-4a,8-dimethyl-2H-phenoxazine-2-one on proliferation of phytohemagglutinin- or anti-human IgM-activated human peripheral blood mononuclear cells*. Tohoku J Exp Med 2002, 196(3): 185.

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5. Maruyama, K. et al. *Highly selective formation of 2-aminophenoxazin-3-one by catalytic oxygenation of o-aminophenol*. Chem Lett 1996, (9): 819.

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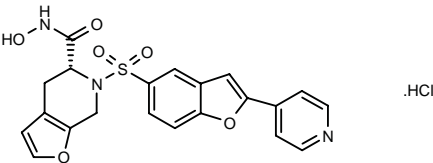
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9. Tomoda, A. et al. *Phenoxazinone synthesis by human hemoglobin*. *Biochim Biophys Acta* 1992, 117(3): 306.

323252

6-[2-(4-Pyridyl)-1-benzofuran-5-ylsulfonyl]-4,5,6,7-tetrahydrofuro[2,3-*c*]pyridine-5(*R*)-carbohydroxamic acid hydrochloride



C21 H17 N3 O6 S . HCl; Mol wt: 475.9072

ACTION – An inhibitor of metalloproteinases with potential in the treatment of cancer, arthritis and atherosclerosis, among other metalloproteinase-mediated conditions.

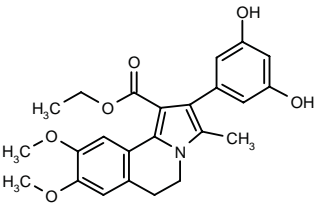
SOURCE – Servier.

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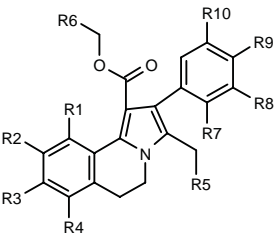
323276

2-(3,5-Dihydroxyphenyl)-8,9-dimethoxy-3-methyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-1-carboxylic acid ethyl ester



C24 H25 N O6; Mol wt: 423.4625

ACTION – An inhibitor of phosphodiesterase type 10A (PDE10A), a recently identified enzyme able to hydrolyze both cAMP and cGMP. Compound demonstrated *in vitro* activity against PDE10A expressed in Sf9 cells, and was also able to inhibit the proliferation of human breast carcinoma MDA-MB-231 cells by approximately 90% at 10 μ M. Potentially useful for the treatment of cancer. Other exemplified compounds are:



Compound	R1	R2	R3	R4	R5	R6	R7	R8	R9	R10	Formula
323277	H	OMe	OMe	H	H	Me	NO2	H	H	OH	C ₂₄ H ₂₄ N ₂ O ₇
323278	H	OMe	OMe	H	H	Me	H	OH	OMe	OMe	C ₂₆ H ₂₉ NO ₇
323279	H	OMe	OMe	H	Me	Me	H	CF3	H	H	C ₂₆ H ₂₆ F ₃ NO ₄
323280	H	OMe	OMe	H	H	Me	H	CF3	H	H	C ₂₅ H ₂₄ F ₃ NO ₄
323281	H	OMe	OMe	H	H	Me	H	NO2	OH	H	C ₂₄ H ₂₄ N ₂ O ₇
323282	H	OMe	OMe	H	H	H	H	OH	OMe	OMe	C ₂₅ H ₂₇ NO ₇
323283	H	H	OMe	OMe	H	H	H	Me	OH	Me	C ₂₅ H ₂₇ NO ₅
323284	OMe	H	H	H	H	Me	H	OMe	OMe	OMe	C ₂₆ H ₂₉ NO ₆
323285	H	H	OCF3	H	H	H	H	Me	OH	Me	C ₂₄ H ₂₂ F ₃ NO ₄
323286	H	OMe	OMe	H	H	Me	H	Cl	H	H	C ₂₄ H ₂₄ ClNO ₄
323287	H	OEt	OMe	H	H	Me	H	H	F	H	C ₂₅ H ₂₆ FNO ₄

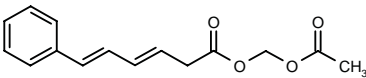
SOURCE – Bayer.

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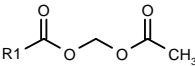
323305

6-Phenyl-3,5-hexadienoic acid acetoxymethyl ester



C15 H16 O4; Mol wt: 260.2874

ACTION – Histone deacetylase inhibitor that was shown to inhibit the proliferation of prostate cancer PC-3 cells with an IC₅₀ of 18 μ M. Potentially useful for the treatment of cancer, gastrointestinal disorders and protozoal infections, and also for wound healing and as an immuno-modulator. Other exemplified acetyloxymethyl esters are:



Compound	R1	Formula
323306	Ph-ethynylene	C ₁₂ H ₁₀ O ₄
323307	CH2SCH2Ph	C ₁₂ H ₁₄ O ₄ S
323308	CH=CHSPh	C ₁₂ H ₁₂ O ₄ S
323309	cyclohexyl-(CH2)3	C ₁₃ H ₂₂ O ₄
323310	CH=CHCH=CHPh	C ₁₄ H ₁₄ O ₄

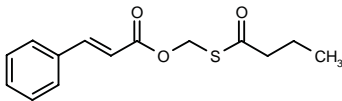
SOURCE – Beacon Laboratories.

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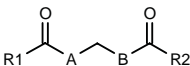
323311

3-Phenyl-2-propenoic acid butyrylsulfanylmethyl ester



C14 H16 O3 S; Mol wt: 264.3434

ACTION – Histone deacetylase inhibitor shown to inhibit the proliferation of prostate cancer PC-3 cells with an IC₅₀ of 30 μM. Claimed for use in the treatment of cancer, wound healing, gastrointestinal disorders, protozoal infections, and also as an immunomodulator. Other exemplified δ-dicarbonyl compounds are:



Compound	R1	R2	A	B	Formula
323312	Pr	CH2OCH2CH2OMe	O	N(Me)	C ₁₁ H ₂₁ NO ₅
323313	CH=CHPh	Pr	O	N(Me)	C ₁₅ H ₁₉ NO ₃
323314	Pr	CH=CHPh	O	N(Me)	C ₁₅ H ₁₉ NO ₃
323315	Pr	CH=CHPh	O	S	C ₁₄ H ₁₆ O ₃ S
323316	Pr	Pr	S	S	C ₉ H ₁₆ O ₂ S ₂
323317	Et	Et	O	S	C ₉ H ₁₆ O ₃ S

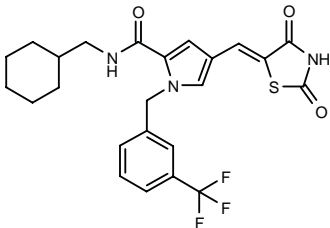
SOURCE – Beacon Laboratories.

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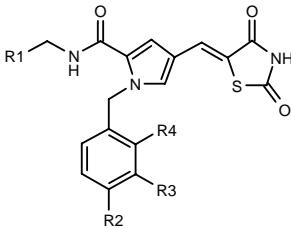
324150

(Z)-N-(Cyclohexylmethyl)-4-(2,4-dioxothiazolidin-5-ylidenemethyl)-1-[3-(trifluoromethyl)benzyl]-1 H-pyrrole-2-carboxamide



C24 H24 F3 N3 O3 S; Mol wt: 491.5316

ACTION – Telomerase inhibitor (IC₅₀ = 2.3 μM) with potential in the treatment of malignant tumors. In human kidney cancer cells, compound reduced telomerase activity by 81% at a concentration of 10 μM. Other exemplified thiazolidine compounds are:



Compound	R1	R2	R3	R4	Formula
324151	CH2CH(Ph)2	H	H	Ph	C ₃₇ H ₃₁ N ₃ O ₃ S
324152	CH2CH(Ph)2	H	H	CH2SO2Ph	C ₃₈ H ₃₃ N ₃ O ₅ S ₂
324153	CH2CH(Ph)2	Me	H	H	C ₃₂ H ₂₉ N ₃ O ₃ S
324154	1-Naph	t-Bu	H	H	C ₃₁ H ₂₉ N ₃ O ₃ S
324155	2-CF3-Ph	H	H	CH2SO2Ph	C ₃₁ H ₂₄ F ₃ N ₃ O ₅ S ₂
324156	3-Cl-Ph	H	H	Me	C ₂₄ H ₂₀ ClN ₃ O ₃ S
324157	cyclohexyl	Br	H	H	C ₂₃ H ₂₄ BrN ₃ O ₃ S
324158	CH2CH(Ph)2	H	2H-tetrazol-5-yl	H	C ₃₂ H ₂₇ N ₇ O ₃ S
324159	4-Me-PhCH2	H	CF3	H	C ₂₈ H ₂₂ F ₃ N ₃ O ₃ S
324160	1-Naph	H	F	H	C ₂₇ H ₂₀ FN ₃ O ₃ S
324161	i-Bu	Cl	Cl	H	C ₂₁ H ₂₁ Cl ₂ N ₃ O ₃ S
324162	1-Naph	H	CN	H	C ₂₈ H ₂₀ N ₄ O ₃ S
324163	3-Cl-Ph	Br	H	H	C ₂₃ H ₁₇ BrClN ₃ O ₃ S

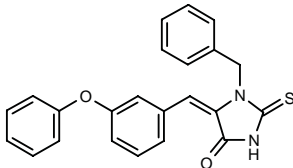
SOURCES – Geron; Kyowa Hakko.

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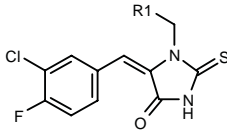
324164

1-Benzyl-5-(3-phenoxybenzylidene)-2-thioxoimidazolidin-4-one



C23 H18 N2 O2 S; Mol wt: 386.4732

ACTION – Telomerase inhibitor, as demonstrated against purified enzyme (IC₅₀ = 2.4 μM) and in human kidney cancer cells (61% inhibition at 30 μM). Potentially useful for the treatment of tumors. Other exemplified 4-oxo-2-thioxoimidazolidine compounds are:



Compound	R1	Formula
324165	2-Me-PhCH2	C ₁₉ H ₁₆ ClFN ₂ OS
324166	4-BuO-Ph	C ₂₁ H ₂₀ ClFN ₂ O ₂ S

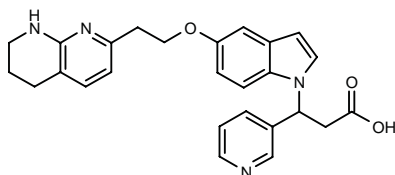
SOURCES – Geron; Kyowa Hakko.

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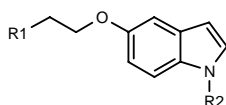
325273

3-(3-Pyridyl)-3-[5-[2-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)ethoxy]-1*H*-indol-1-yl]propionic acid



C26 H26 N4 O3; Mol wt: 442.5164

ACTION – Integrin $\alpha_v\beta_3$ receptor antagonist ($IC_{50} = 0.24$ nM), potentially useful for the treatment of cancer, osteoporosis, restenosis, inflammation, macular degeneration, diabetic retinopathy, rheumatoid arthritis and sickle cell anemia. Other applications include CNS disorders associated with ischemia, Alzheimer's disease, Parkinson's disease and schizophrenia. Other exemplified substituted indoles are:



Compound	R1	R2	Formula
325275	2-Pyr-NHCH2	CH2CH2CO2 ⁻ NH4 ⁺	C ₁₉ H ₂₄ N ₄ O ₃
325276	2-Pyr-NHCH2	trans-2-(CO2HCH2)-cyclopropyl	C ₂₁ H ₂₃ N ₃ O ₃
325279	6-MeNH-2-Pyr	CH2CH2CO2H	C ₁₉ H ₂₁ N ₃ O ₃
325281	2-Pyr-NHCH2	CH2CH(Me)CO2H	C ₂₀ H ₂₃ N ₃ O ₃
325283	5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl	CH(Pr)CH2CO2H	C ₂₄ H ₂₉ N ₃ O ₃
325285	5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl	CH2CH2CO2H	C ₂₁ H ₂₃ N ₃ O ₃

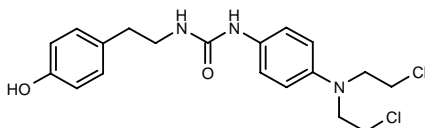
SOURCE – 3-Dimensional Pharmaceuticals.

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325441

N-[4-[Bis(2-chloroethyl)amino]phenyl]-*N'*-[2-(4-hydroxyphenyl)ethyl]urea



C19 H23 Cl2 N3 O2; Mol wt: 396.3157

ACTION – Urea prodrug for melanocyte-directed enzyme prodrug therapy (MDEPT). The prodrug acts as a substrate for the melanocyte enzyme tyrosinase and, upon exposure to the enzyme, releases a cytotoxic nitrogen mustard. The prodrug exhibited good stability in bovine and human sera under physiological and hydrolytic conditions.

SOURCES – Imperial College of Science, Technology and Medicine, London (GB); University of Reading, Reading (GB).

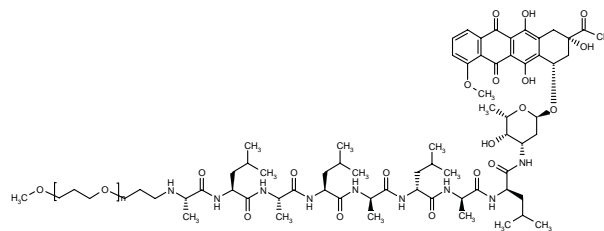
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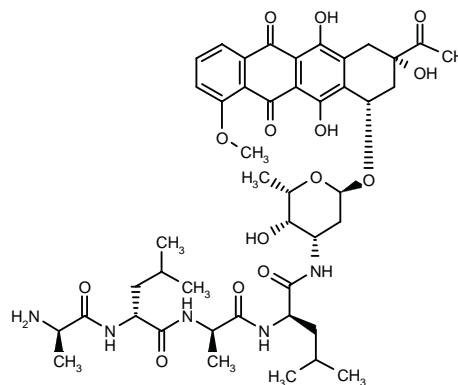
2. Jordan, A.M. et al. *Synthesis and analysis of urea and carbamate prodrugs as candidates for melanocyte-directed enzyme prodrug therapy (MDEPT)*. Bioorg Med Chem 2002, 10(8): 2625.

325542

N-(*N*-Polyethyleneglycol-L-alanyl-L-leucyl-L-alanyl-L-leucyl-D-alanyl-D-leucyl-D-alanyl-D-leucyl)daunorubicin



ACTION – Prodrug of an antitumor agent containing an antitumor intravascular coagulation-inducing moiety, a heparin-binding moiety and an uncharged or negatively charged masking moiety. This prodrug was designed to release the heparin-binding antitumor drug conjugate at the tumor site, thus displaying reduced toxicity in normal tissues. The active drug derived from this prodrug is:



325578: C45 H61 N5 O14

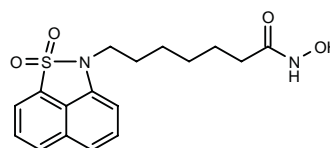
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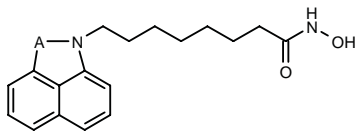
325601

7-(1,1-Dioxo-2*H*-naphtho[1,8-*cd*]isothiazol-2-yl)heptano-hydroxamic acid



C17 H20 N2 O4 S; Mol wt: 348.4210

ACTION – Histone deacetylase (HDAC) inhibitor (90% inhibition at 10 nM) for use in the treatment of cell proliferative disorders such as cancer. Other exemplified tricyclic derivatives are:



Compound	A	Formula
325603	SO2	C ₁₈ H ₂₂ N ₂ O ₄ S
325604	CO	C ₁₉ H ₂₂ N ₂ O ₃

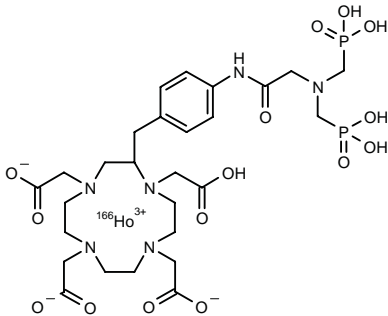
SOURCE – Roche.

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1. Georges, G. et al. (F. Hoffmann-La Roche AG) *Tricyclic lactam and sultam derivs. and their use as histone deacetylase inhibitors*. WO 0262773.

325627

Tetrahydrogen 2-[4-[N,N-bis(phosphonomethyl)glycyl-amino]benzyl]-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetato(7-)]holmate(4-)-166Ho



C27 H41 Ho N6 O15 P2; Mol wt: 917.5959

ACTION – A complex comprised of a nitrogen-containing cycloalkyl derivative and holmium-166 as a therapeutic radionuclide. Claimed for use in the treatment of cancer, bone pain and bone-related disorders including Crohn’s disease, rheumatoid arthritis, multiple sclerosis, osteoporosis, osteopenia, osteomyelitis, Paget’s disease, sickle cell anemia and lysosomal or peroxisomal storage disease, as well as for suppressing bone marrow. The invention also includes complexes containing detectable radionuclides (technetium-99m, rhutenium-97, indium-111, gallium-67 or -68 and lead-203) that are reportedly useful as diagnostic agents for detecting the presence or absence of calcified tissue.

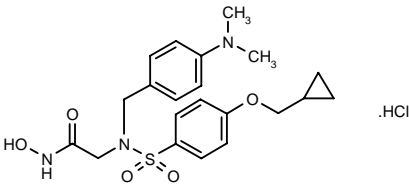
SOURCE – NeoRx.

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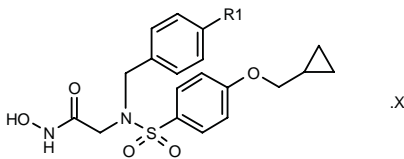
325986

2-[N-[4-(Cyclopropylmethoxy)phenylsulfonyl]-N-[4-(dimethylamino)benzyl]amino]acetohydroxamic acid hydrochloride



C21 H27 N3 O5 S . HCl; Mol wt: 469.9872

ACTION – Matrix metalloproteinase (MMP) inhibitor, particularly active against membrane-type 1 MMP (MT1-MMP), MMP-2 (gelatinase A) and/or MMP-9 (gelatinase B), with IC₅₀ values of 4.67, 3.29 and 2.57 nM, respectively, against MT1-MMP, MMP-2 and MMP-9 versus 1770 nM against MMP-1 (interstitial collagenase). Potentially useful for the treatment of cancer, chronic obstructive pulmonary disease, brain edema and asthma. Other specifically claimed compounds are:



Compound	R1	X	Formula
325988	2H-1,2,3-triazol-2-yl		C ₂₁ H ₂₃ N ₅ O ₅ S
325989	2H-1,2,3-triazol-2-yl	HCl	C ₂₁ H ₂₃ N ₅ O ₅ S.HCl
325990	N(Me)2		C ₂₁ H ₂₇ N ₃ O ₅ S
325991	1,2,3-triazol-1-yl		C ₂₁ H ₂₃ N ₅ O ₅ S
325992	1,2,4-triazol-4-yl		C ₂₁ H ₂₃ N ₅ O ₅ S
325993	N(Et)2		C ₂₃ H ₃₁ N ₃ O ₅ S
325994	N(Et)2	HCl	C ₂₃ H ₃₁ N ₃ O ₅ S.HCl

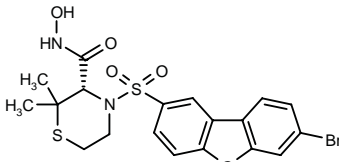
SOURCE – Novartis.

REFERENCES

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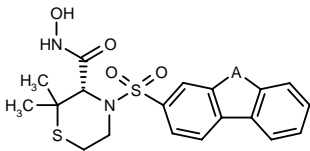
326058

4-(7-Bromodibenzo[b,d]furan-2-ylsulfonyl)-2,2-dimethyl-thiomorpholine-3(S)-carbohydroxamic acid

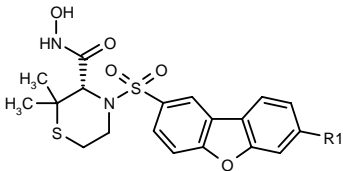


C19 H19 Br N2 O5 S2; Mol wt: 499.4041

ACTION – Matrix metalloproteinase (MMP) inhibitor that demonstrated *in vitro* activity against MMP-1 (interstitial collagenase), MMP-2 (gelatinase A), MMP-3 (stromelysin 1), MMP-7 (matrilysin), MMP-9 (gelatinase B), MMP-13 (collagenase 3) and MMP-14 (MT-1 MMP). Potentially useful for the treatment of cancer, rheumatoid arthritis, osteoarthritis, heart failure and inflammation. Other exemplified tricyclic sulfonamides are:



Compound	A	Formula
326059	O	C ₁₉ H ₂₀ N ₂ O ₅ S ₂
326060	CH2	C ₂₀ H ₂₂ N ₂ O ₄ S ₂



Compound	R1	Formula
326061	H	C ₁₉ H ₂₀ N ₂ O ₅ S ₂
326062	CO2Me	C ₂₁ H ₂₂ N ₂ O ₇ S ₂
326063	NO2	C ₁₉ H ₁₉ N ₃ O ₇ S ₂

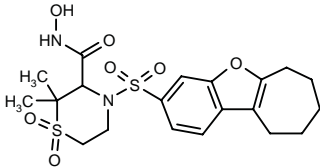
SOURCE – Pfizer.

REFERENCES

1. O'Brien, P.M. et al. (Pfizer Inc.) *Tricyclic sulfonamides useful as matrix metalloproteinase inhibitors*. EP 1233017.

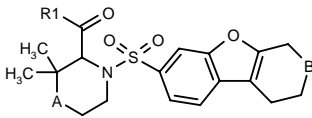
326065

2,2-Dimethyl-1,1-dioxo-4-(7,8,9,10-tetrahydro-6*H*-benzo-[*b*]cyclohepta[*d*]furan-3-ylsulfonyl)thiomorpholine-3-carboxohydroxamic acid



C20 H26 N2 O7 S2; Mol wt: 470.5644

ACTION – Matrix metalloproteinase (MMP) inhibitor that demonstrated *in vitro* activity against MMP-1 (interstitial collagenase), MMP-2 (gelatinase A), MMP-3 (stromelysin 1), MMP-7 (matrilysin), MMP-9 (gelatinase B), MMP-13 (collagenase 3) and MMP-14 (MT-1 MMP). Potentially useful for the treatment of cancer, rheumatoid arthritis, osteoarthritis, heart failure and inflammation. Other exemplified tricyclic sulfonamides are:



Compound	R1	A	B	Isomer	Formula
326066	OH	S	-CH2-	S	C ₁₉ H ₂₃ NO ₅ S ₂
326067	NHOH	S	-CH2-	S	C ₁₉ H ₂₄ N ₂ O ₅ S ₂
326068	OH	SO2	-(CH2)2-		C ₂₀ H ₂₅ NO ₇ S ₂

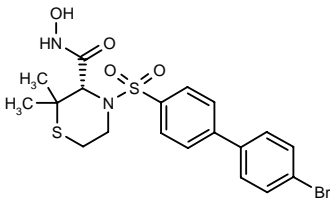
SOURCE – Pfizer.

REFERENCES

1. O'Brien, P.M. and Sliskovic, D.R. (Pfizer Inc.) *Tricyclic biphenyl sulfonamide matrix metalloproteinase inhibitors*. EP 1233018, JP 2002275181.

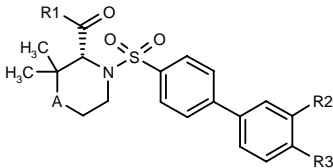
326069

4-(4'-Bromobiphenyl-4-ylsulfonyl)-2,2-dimethylthiomorpholine-3(S)-carboxhydroxamic acid



C19 H21 Br N2 O4 S2; Mol wt: 485.4209

ACTION – Matrix metalloproteinase (MMP) inhibitor that demonstrated *in vitro* activity against MMP-1 (interstitial collagenase), MMP-2 (gelatinase A), MMP-3 (stromelysin 1), MMP-7 (matrilysin), MMP-9 (gelatinase B), MMP-13 (collagenase 3) and MMP-14 (MT-1 MMP). Potentially useful for the treatment of cancer, rheumatoid arthritis, osteoarthritis, heart failure and inflammation. Other exemplified biphenyl sulfonamides are:



Compound	R1	R2	R3	A	Formula
326070	NHOH	H	Br	SO2	C ₁₉ H ₂₁ BrN ₂ O ₆ S ₂
326071	OH	H	SMe	S	C ₂₀ H ₂₃ NO ₄ S ₃
326072	OH	H	Ph	S	C ₂₅ H ₂₅ NO ₄ S ₂
326073	OH	H	OEt	S	C ₂₁ H ₂₅ NO ₅ S ₂
326074	OH	F	Ph	S	C ₂₅ H ₂₄ FNO ₄ S ₂

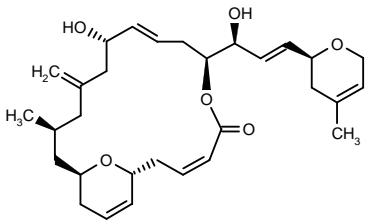
SOURCE – Pfizer.

REFERENCES

1. Barvian, N.C. et al. (Pfizer Inc.) *Biphenyl sulfonamides useful as matrix metalloproteinase inhibitors*. EP 1233016, JP 2002275168.

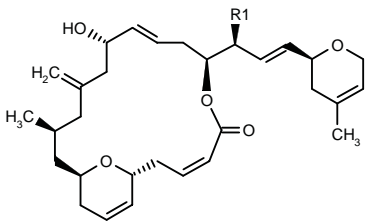
326221

(1*R*,7*S*,11*S*,15*S*,17*R*)-11-Hydroxy-7-[1(*S*)-hydroxy-3-[4-methyl-3,6-dihydro-2*H*-pyran-2(*S*)-yl]-2(*E*)-propenyl]-15-methyl-13-methylene-6,21-dioxabicyclo[15.3.1]henicosa-3,9,19-trien-5-one



C30 H42 O6; Mol wt: 498.6558

ACTION – Synthetic analogue of the macrolide compound laulimalide, reported to display antiproliferative activity. Potentially useful for the treatment of cancer, psoriasis, eczema, dermatitis, multiple sclerosis and rheumatoid arthritis. Other specifically claimed compounds are:



Compound	R1	Formula
326222	H	C ₃₀ H ₄₂ O ₅
326223	OMe	C ₃₁ H ₄₄ O ₆

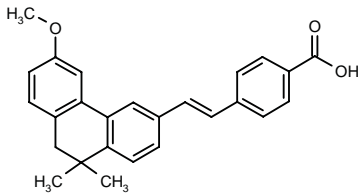
SOURCE – Kosan Biosciences.

REFERENCES

1. Ashley, G. and Metcalf, B. (Kosan Biosciences, Inc.) *Laulimalide derivs.* WO 0264589.

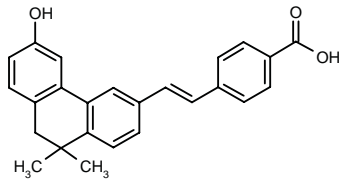
326469

4-[(*E*)-2-(6-Methoxy-10,10-dimethyl-9,10-dihydrophenanthren-3-yl)vinyl]benzoic acid



C26 H24 O3; Mol wt: 384.4726

ACTION – Agent with retinoid-like activity that showed K_d values of 1.1, 1.6 and 10.6 nM, respectively, at retinoic acid receptors RAR α , RAR β and RAR γ in radioligand binding assays. It was also found to activate these RAR receptor subtypes in a reporter gene assay with respective EC₅₀s of 0.02, 0.005 and 1.9 nM. Compound demonstrated cytotoxic activity against human breast cancer T-47D and human cervical carcinoma HT-3 cells. Potentially useful for the treatment of cancer, as well as inflammatory and rheumatic diseases and proliferative skin disorders. Another exemplified compound is:



326471: C25 H22 O3

SOURCE – Bristol-Myers Squibb.

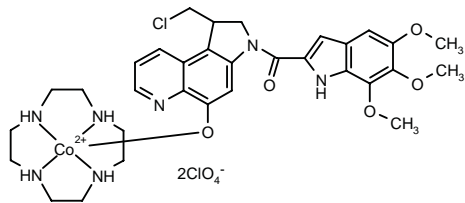
REFERENCES

1. Ericsson, A. et al. (Bristol-Myers Squibb Co.) *Cpds. having retinoid-like activity.* WO 0265984.

SN-27892

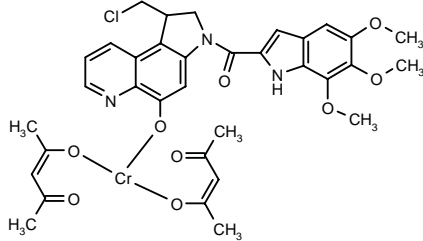
324943

[1-(Chloromethyl)-3-(5,6,7-trimethoxy-1*H*-indol-2-ylcarbonyl)-2,3-dihydro-1*H*-pyrrolo[3,2-*f*]quinolin-5-olato- κ O][1,4,7,10-tetraazacyclododecane- κ N¹, κ N⁴, κ N⁷, κ N¹⁰]-cobalt(III) diperchlorate

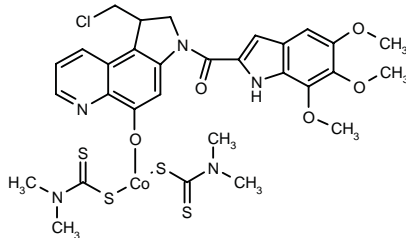


C32 H41 Cl Co N7 O5 . 2 Cl O4; Mol wt: 897.0039

ACTION – Cobalt complex that acts as a prodrug of a known antitumor agent and can be activated either under hypoxic conditions or by ionizing radiation. SN-27892 displayed reduced cytotoxicity as compared with the corresponding active compound against AA8, UV4, EMT6 and SK-OV-3 cells. Following activation under hypoxic conditions, the prodrug gave IC₅₀ values of 0.38, 1.7 and 1.7 nM, respectively, against the cancer cell lines A-549, SK-OV-3 and WiDr-2. Other exemplified cobalt and chromium complexes are:



324945: C34 H35 Cl Cr N3 O9



324946: C30 H33 Cl Co N5 O5 S4

SOURCE – University of Auckland, Auckland (NZ).

REFERENCES

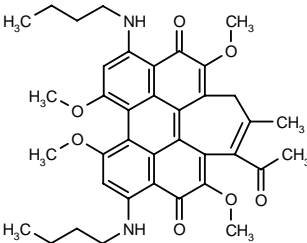
1. Denny, W.A. et al. (Auckland Uniservices Ltd.) *Anti-cancer 2,3-dihydro-1H-pyrrolo-[2,3-f]quinoline complexes of cobalt and chromium*. WO 0259122.

RADIATION THERAPY

HBBA-R2

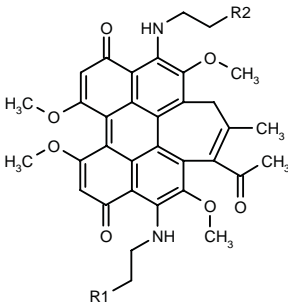
325452

3-Acetyl-6,11-bis(butylamino)-4,8,9,13-tetramethoxy-2-methyl-5,12-dihydro-1*H*-cyclohepta[*ghi*]perylene-5,12-dione



C38 H42 N2 O7; Mol wt: 638.7568

ACTION – Photosensitizing and sonosensitizing agent with the ability to modulate the activity of immuno-therapeutic agents. Potentially useful for the treatment of cancer, as well as autoimmune diseases and viral, bacterial and fungal infections. Other exemplified compounds are:



Compound	R1	R2	Formula
HBEA-R1 [325456]	OH	OH	C ₃₄ H ₃₄ N ₂ O ₉
HBDP-R1 [325524]	CH2N(Me)2	CH2N(Me)2	C ₄₀ H ₄₆ N ₄ O ₇

SOURCES – University of Alberta, Edmonton, AB (CA); Altachem.

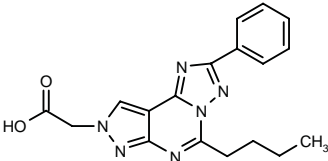
REFERENCES

1. Leveugle, B. (Altachem Pharma Ltd.) *Perylenequinones for use with immunotherapy agents*. WO 0260482.
2. Miller, G.G. and Lown, J.W. (University of Alberta) *Perylenequinones for use as photosensitizers and sonosensitizers*. WO 0260483.

OCULAR MEDICATIONS

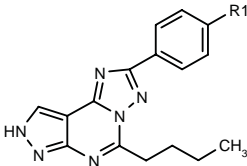
326261

2-(5-Butyl-2-phenyl-8*H*-pyrazolo[4,3-*e*][1,2,4]triazolo-[1,5-*c*]pyrimidin-8-yl)acetic acid

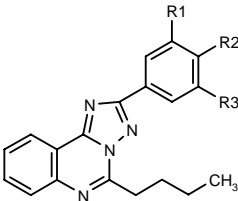


C18 H18 N6 O2; Mol wt: 350.3802

ACTION – Agent with affinity for adenosine A₃ receptors that displayed IC₅₀ values of 32 and > 10,000 nM, respectively, at A₃ and A₂ receptors expressed in human endothelial HEK-293 cells. Potentially useful for the treatment of glaucoma. Other exemplified compounds are:



Compound	R1	Formula
326262	H	C ₁₆ H ₁₆ N ₆
326265	F	C ₁₆ H ₁₅ FN ₆
326266	Cl	C ₁₆ H ₁₅ ClN ₆
326267	Me	C ₁₇ H ₁₈ N ₆



Compound	R1	R2	R3	Formula
326264	OMe	OMe	OMe	C ₂₂ H ₂₄ N ₄ O ₃
326269	H	Br	H	C ₁₉ H ₁₇ BrN ₄

SOURCE – Otsuka.

REFERENCES

1. Okamura, T. et al. (Otsuka Pharmaceutical Co., Ltd.) *Triazoloquinazoline and pyrazolotriazolopyrimidine derivs., medicinal compsns., adenosine A3 receptor affinity agents, ocular tension lowering agents, preparations for preventing and treating glaucoma and method of lowering ocular tension*. WO 0262801.

SOURCE – University of Auckland, Auckland (NZ).

REFERENCES

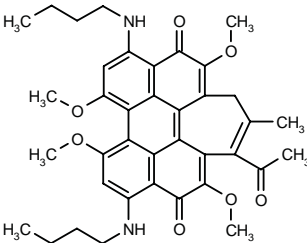
1. Denny, W.A. et al. (Auckland Uniservices Ltd.) *Anti-cancer 2,3-dihydro-1H-pyrrolo-[2,3-f]quinoline complexes of cobalt and chromium*. WO 0259122.

RADIATION THERAPY

HBBA-R2

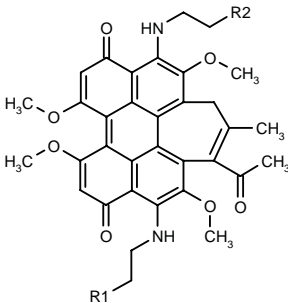
325452

3-Acetyl-6,11-bis(butylamino)-4,8,9,13-tetramethoxy-2-methyl-5,12-dihydro-1*H*-cyclohepta[*ghi*]perylene-5,12-dione



C38 H42 N2 O7; Mol wt: 638.7568

ACTION – Photosensitizing and sonosensitizing agent with the ability to modulate the activity of immuno-therapeutic agents. Potentially useful for the treatment of cancer, as well as autoimmune diseases and viral, bacterial and fungal infections. Other exemplified compounds are:



Compound	R1	R2	Formula
HBEA-R1 [325456]	OH	OH	C ₃₄ H ₃₄ N ₂ O ₉
HBDP-R1 [325524]	CH2N(Me)2	CH2N(Me)2	C ₄₀ H ₄₆ N ₄ O ₇

SOURCES – University of Alberta, Edmonton, AB (CA); Altachem.

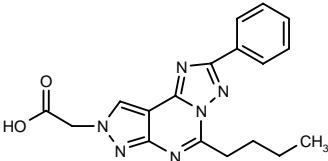
REFERENCES

1. Leveugle, B. (Altachem Pharma Ltd.) *Perylenequinones for use with immunotherapy agents*. WO 0260482.
2. Miller, G.G. and Lown, J.W. (University of Alberta) *Perylenequinones for use as photosensitizers and sonosensitizers*. WO 0260483.

OCULAR MEDICATIONS

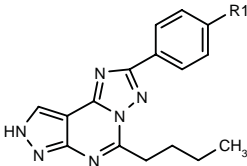
326261

2-(5-Butyl-2-phenyl-8*H*-pyrazolo[4,3-*e*][1,2,4]triazolo-[1,5-*c*]pyrimidin-8-yl)acetic acid

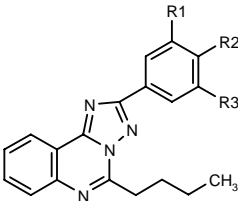


C18 H18 N6 O2; Mol wt: 350.3802

ACTION – Agent with affinity for adenosine A₃ receptors that displayed IC₅₀ values of 32 and > 10,000 nM, respectively, at A₃ and A₂ receptors expressed in human endothelial HEK-293 cells. Potentially useful for the treatment of glaucoma. Other exemplified compounds are:



Compound	R1	Formula
326262	H	C ₁₆ H ₁₆ N ₆
326265	F	C ₁₆ H ₁₅ FN ₆
326266	Cl	C ₁₆ H ₁₅ ClN ₆
326267	Me	C ₁₇ H ₁₈ N ₆



Compound	R1	R2	R3	Formula
326264	OMe	OMe	OMe	C ₂₂ H ₂₄ N ₄ O ₃
326269	H	Br	H	C ₁₉ H ₁₇ BrN ₄

SOURCE – Otsuka.

REFERENCES

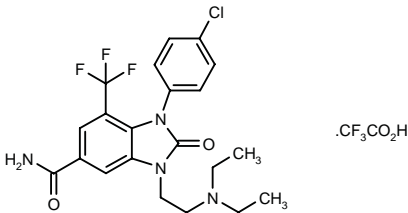
1. Okamura, T. et al. (Otsuka Pharmaceutical Co., Ltd.) *Triazoloquinazoline and pyrazolotriazolopyrimidine derivs., medicinal compsns., adenosine A3 receptor affinity agents, ocular tension lowering agents, preparations for preventing and treating glaucoma and method of lowering ocular tension*. WO 0262801.

METABOLIC DRUGS

TREATMENT OF BONE DISEASES

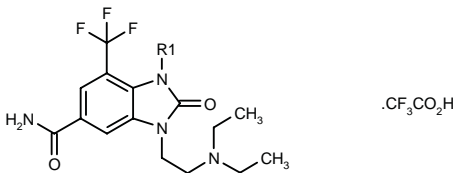
325872

1-(4-Chlorophenyl)-3-[2-(diethylamino)ethyl]-2-oxo-7-(trifluoromethyl)-2,3-dihydro-1*H*-benzimidazole-5-carboxamide trifluoroacetate



C21 H22 Cl F3 N4 O2 . C2 H F3 O2; Mol wt: 568.8997

ACTION – Growth hormone (GH) secretion-promoting agent, as demonstrated by a 3-fold increase in GH secretion in rat hypophysis preparations at 10 μ M. Potentially useful for the treatment of disorders associated with GH deficiency such as osteoporosis, wound healing, bone repair, growth retardation and renal failure, as well as for stimulating the immune system and preventing anabolic side effects of glucocorticoid treatment. Other exemplified benzimidazolidinone derivatives are:



Compound	R1	Formula
325874	3-Cl-PhCH2	C ₂₂ H ₂₄ ClF ₃ N ₄ O ₂ ·C ₂ HF ₃ O ₂
325875	2-Cl-PhCH2	C ₂₂ H ₂₄ ClF ₃ N ₄ O ₂ ·C ₂ HF ₃ O ₂
325876	2,4-(Cl) ₂ -Ph	C ₂₁ H ₂₁ Cl ₂ F ₃ N ₄ O ₂ ·C ₂ HF ₃ O ₂
325877	3-CF ₃ -PhCH2	C ₂₃ H ₂₄ F ₆ N ₄ O ₂ ·C ₂ HF ₃ O ₂
325878	2-Me-PhCH2	C ₂₃ H ₂₇ F ₃ N ₄ O ₂ ·C ₂ HF ₃ O ₂

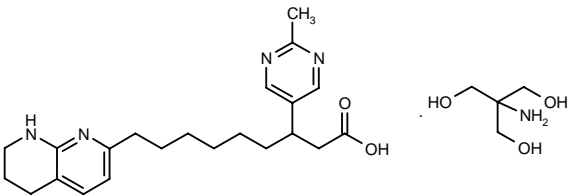
SOURCE – Sumitomo Pharmaceuticals.

REFERENCES

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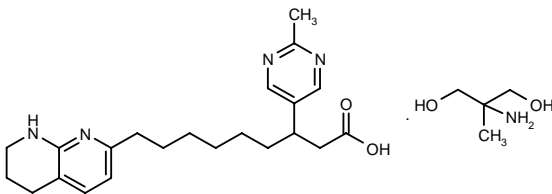
326224

3-(2-Methylpyrimidin-5-yl)-9-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)nonanoic acid 2-amino-2-(hydroxymethyl)propane-1,3-diol salt



C22 H30 N4 O2 . C4 H11 N O3; Mol wt: 503.6399

ACTION – An amine salt of a previously known $\alpha_v\beta_3$ antagonist, particularly useful for the treatment of osteoporosis. Further applications include restenosis, diabetic retinopathy, macular degeneration, atherosclerosis, arthritis and cancer. Another specifically claimed salt is:



326225: C22 H30 N4 O2 . C4 H11 N O

SOURCE – Merck & Co.

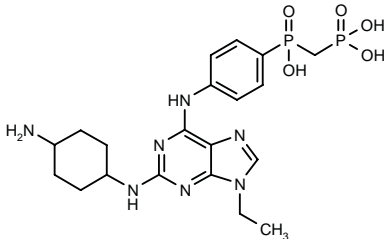
REFERENCES

1. Humphrey, G.R. et al. (Merck & Co., Inc.) *Amine salts of an integrin receptor antagonist.* US 6444680.

AP-23317

309598

[4-[2-(4-Aminocyclohexylamino)-9-ethyl-9*H*-purin-6-ylamino]phenyl](hydroxy)phosphorylmethyl]phosphonic acid



C20 H29 N7 O5 P2; Mol wt: 509.4411

ACTION – Potent, bone-targeted Src tyrosine kinase inhibitor (IC₅₀ = 45 nM) with high selectivity over other families of kinases including cyclin-dependent kinases (CDKs), mitogen-activated protein kinase (MAPK) and MEK kinases, as well as serine/threonine kinases. *In vivo*, compound (1-10 mg/kg s.c. b.i.d.) significantly prevented bone resorption in a model of parathyroid hormone (PTH)-induced hypercalcemia in rats and in a model of ovariectomy-induced bone loss in mice. Potentially useful for the treatment of osteoporosis.

SOURCE – Ariad.

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1. Weigele, M. et al. (Ariad Pharmaceuticals Inc.) *Novel purines*. WO 0144260.

2. Weigele, M. et al. (Ariad Pharmaceuticals Inc.) *Purine derivs*. US 2002068721.

3. Weigele, M. et al. (Ariad Pharmaceuticals Inc.) *Purine derivs*. WO 0144259.

4. Byce, B. et al. *Novel bone-targeted Src tyrosine kinase inhibitors prevent bone loss and stimulate osteoblast activity*. J Bone Miner Res 2001, 16(Suppl. 1): Abst 1048.

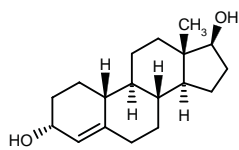
5. Dalgarno, D. et al. *Design of novel bone-targeting chemical groups and their exploitation in the discovery of anti-resorptive Src tyrosine kinase inhibitors*. J Bone Miner Res 2001, 16(Suppl. 1): Abst M311.

6. Naugle, J.L. and Wang, Y. *Development of novel Src tyrosine kinase inhibitors for the treatment of osteoporosis*. 224th ACS Natl Meet (Aug 18-22, Boston) 2002, Abst MEDI 369.

ESTREN

328241

Estr-4-ene-3α,17β-diol



C18 H28 O2; Mol wt: 276.4172

ACTION – Nongenotropic sex steroid receptor ligand able to increase bone mass and strength, serum osteocalcin levels and the number of osteoblasts on the trabeculae in ovariectomized (OVX) female mice. It was at least as effective as estradiol in OVX females and dihydrotestosterone in orchidectomized males in preserving global and spinal bone mineral density. Unlike estradiol or dihydrotestosterone, the compound did not affect classical transcription and therefore had no effect on reproductive organs or breast cancer cells. Potentially useful for the prevention of osteoporosis.

SOURCE – University of Arkansas, Fayetteville, AR (US).

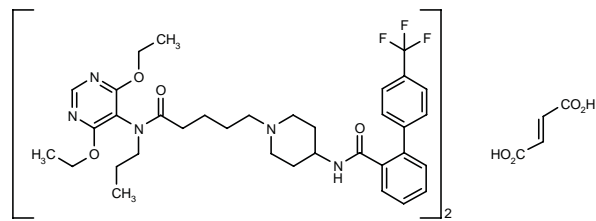
REFERENCES

1. Kousteni, S. et al. *Reversal of bone loss in mice by nongenotropic signaling of sex steroids*. Science 2002, 298(5594): 843.

TREATMENT OF LIPOPROTEIN DISORDERS

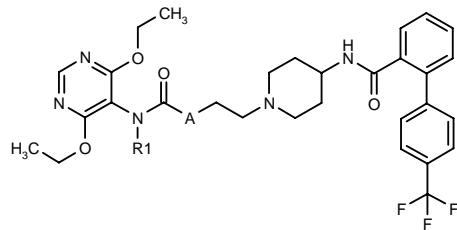
325650

N-[1-[4-[N-(4,6-Diethoxypyrimidin-5-yl)-N-propylcarbamoyl]butyl]piperidin-4-yl]-4'-(trifluoromethyl)biphenyl-2-carboxamide hemifumarate

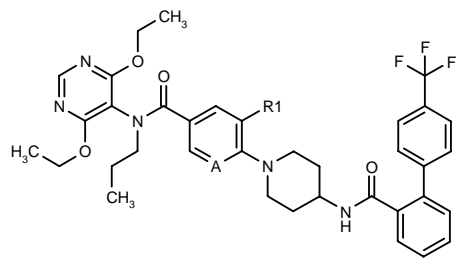


2 C35 H44 F3 N5 O4 . C4 H4 O4; Mol wt: 1427.5870

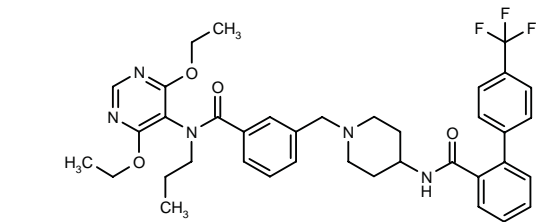
ACTION – Inhibitor of microsomal triglyceride transfer protein (MTP) and apolipoprotein B (apo B) secretion (IC₅₀ = 0.0029 nM) with triglyceride- and cholesterol-lowering activity. Potentially useful for the treatment of hyperlipidemia and arteriosclerosis. Other exemplified anilide derivatives are:



Compound	R1	A	Formula
325651	Bu	-(CH2)2-	C ₃₆ H ₄₆ F ₃ N ₅ O ₄
325652	Et	-(CH2)2-	C ₃₄ H ₄₂ F ₃ N ₅ O ₄
325653	Et	-CH2-	C ₃₃ H ₄₀ F ₃ N ₅ O ₄
325654	Et	bond	C ₃₂ H ₃₈ F ₃ N ₅ O ₄
325655	i-Pr	-CH2-	C ₃₄ H ₄₂ F ₃ N ₅ O ₄
325657	Pr	-(CH2)2-	C ₃₅ H ₄₄ F ₃ N ₅ O ₄



Compound	R1	A	Formula
325658	H	N	C ₃₆ H ₃₉ F ₃ N ₆ O ₄
325660	NO2	CH	C ₃₇ H ₃₉ F ₃ N ₆ O ₆



325661: C38 H42 F3 N5 O4

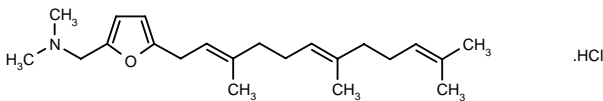
SOURCE – Wakunaga.

REFERENCES

1. Yokomoto, M. et al. (Wakunaga Pharmaceutical Co., Ltd.) *Medicines containing novel anilide derivs. or their salts.* JP 2002212179.

325705

N,N-Dimethyl-*N*-[5-(3,7,11-trimethyldodeca-2,6,10-trienyl)furan-2-ylmethyl]amine hydrochloride



C22 H35 N O . HCl; Mol wt: 365.9854

ACTION – Lipid metabolism improver that inhibits epoxysqualene-lanosterol cyclase (lanosterol synthase, OSLC) and squalene synthase with respective IC₅₀ values of 0.11 and 9.6 μM. Compound inhibited cholesterol biosynthesis in HepG2 cells by 91% at 5 μM. Potentially useful for the treatment of hyperlipidemia.

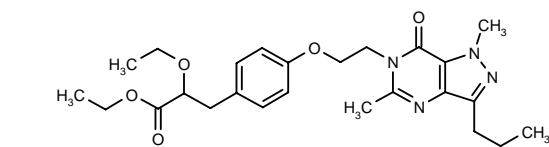
SOURCE – Takeda.

REFERENCES

1. Takaya, M. et al. (Takeda Chemical Industries, Ltd.) *Lipid metabolism improvers.* JP 2002212177.

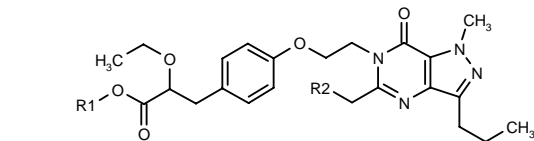
325717

3-[4-[2-(1,5-Dimethyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-*d*]pyrimidin-6-yl)ethoxy]phenyl]-2-ethoxypropionic acid ethyl ester



C25 H34 N4 O5; Mol wt: 470.5666

ACTION – Peroxisome proliferator-activated receptor PPARα and PPARγ agonist that is able to lower plasma levels of glucose, triglycerides, total cholesterol, LDL cholesterol, VLDL cholesterol and free fatty acids. It was shown to activate PPARα and PPARγ receptors in a luciferase reporter gene assay. *In vivo*, compound demonstrated blood glucose- and triglyceride-lowering activity following oral administration to mice. Potentially useful for the treatment of hyperlipidemia, hypercholesterolemia, hyperglycemia, osteoporosis, obesity, glucose intolerance, leptin resistance and insulin resistance. Other exemplified arylcarboxylic acids are:



Compound	R1	R2	Formula
325718	Et	Me	C ₂₆ H ₃₆ N ₄ O ₅
325719	H	Me	C ₂₄ H ₃₂ N ₄ O ₅
325720	H	H	C ₂₃ H ₃₀ N ₄ O ₅
325722	Et	Et	C ₂₇ H ₃₈ N ₄ O ₅

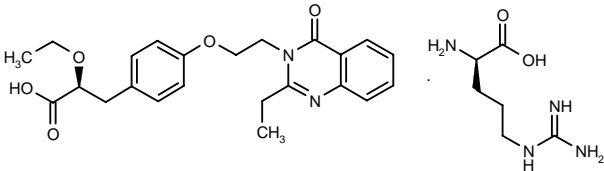
SOURCE – Dr. Reddy’s Research Foundation.

REFERENCES

1. Saibal, K.D. et al. (Dr. Reddy’s Research Foundation) *Aryl subst. alkylcarboxylic acids as hypocholesterolemic agents.* WO 0262799.

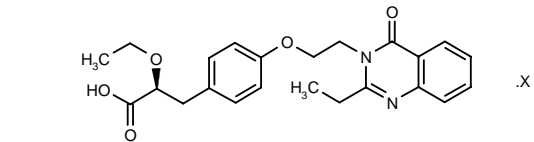
325724

(–)-2(*S*)-Ethoxy-3-[4-[2-(2-ethyl-4-oxo-3,4-dihydroquinazolin-3-yl)ethoxy]phenyl]propionic acid arginine salt

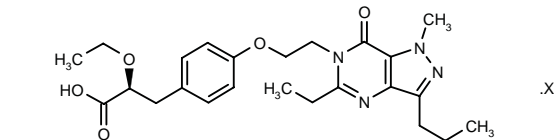


C23 H26 N2 O5 . C6 H14 N4 O2; Mol wt: 584.6700

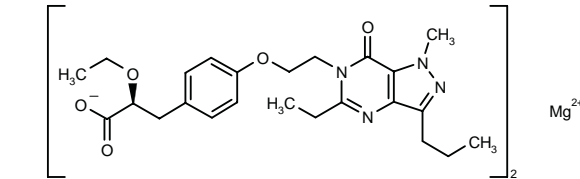
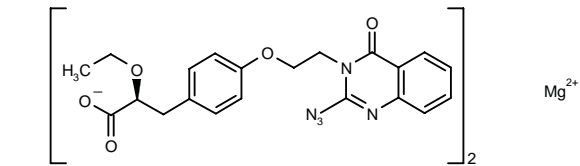
ACTION – Peroxisome proliferator-activated receptor PPARα and PPARγ agonist that is able to lower plasma levels of glucose, triglycerides, total cholesterol, LDL cholesterol, VLDL cholesterol and free fatty acids. It was shown to activate PPARα and PPARγ receptors in a luciferase reporter gene assay. *In vivo*, compound demonstrated blood glucose- and triglyceride-lowering activity following oral administration to mice. Potentially useful for the treatment of hyperlipidemia, hypercholesterolemia, hyperglycemia, osteoporosis, obesity, glucose intolerance, leptin resistance and insulin resistance. Other exemplified compounds are:



Compound	X	Formula
325727	2-Ph-glycinol	C ₂₃ H ₂₆ N ₂ O ₅ ·C ₈ H ₁₁ NO
325728	dicyclohexylamine	C ₂₃ H ₂₆ N ₂ O ₅ ·C ₁₂ H ₂₃ N



Compound	X	Formula
325735	1,1-(Me)2-biguanide	C ₂₄ H ₃₂ N ₄ O ₅ ·C ₄ H ₁₁ N ₅
325736	lysine	C ₂₄ H ₃₂ N ₄ O ₅ ·C ₆ H ₁₄ N ₂ O



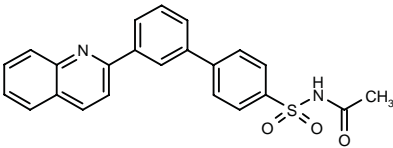
SOURCE – Dr. Reddy’s Research Foundation.

REFERENCES

1. Gaddam, O.R. et al. (Dr. Reddy’s Research Foundation) *Pharmaceutically acceptable salts of heterocyclic cpds.* WO 0262798.

325868

N-Acetyl-3’-(2-quinolinyl)biphenyl-4-sulfonamide



C23 H18 N2 O3 S; Mol wt: 402.4722

ACTION – Agent with the ability to increase the expression of the LDL receptor gene, with serum cholesterol-lowering activity. It was shown to stimulate the expression of LDL receptor genes in HepG2 cells at 0.15 μM. Potentially useful for the treatment of hyperlipidemia.

SOURCE – Sumitomo Pharmaceuticals.

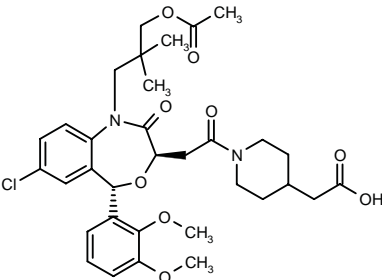
REFERENCES

1. Ueno, Y. et al. (Sumitomo Pharmaceuticals Co., Ltd.) *Triaryl cpds. and utilization thereof.* JP 2002226464, WO 0260876.

TAK-475

321435

2-[1-[2-[1-(3-Acetoxy-2,2-dimethylpropyl)-7-chloro-5(S)-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3(R)-yl]acetyl]piperidin-4-yl]acetic acid



C33 H41 Cl N2 O9; Mol wt: 645.1449

ACTION – Squalene synthase (farnesyl-diphosphate farnesyltransferase) inhibitor (IC₅₀ = 78 nM in HepG2 cells), proven to inhibit cholesterol synthesis in rat liver (ED₅₀ = 2.9 mg/kg p.o.) and to reduce plasma non-HDL cholesterol and triglyceride levels in marmosets and hyperlipidemic rabbit models. Pharmacokinetic studies in rats showed that orally administered compound rapidly hydrolyzed to the deacetylated metabolite, which was mainly distributed to the liver. Potentially useful for the treatment of hyperlipidemia and atherosclerosis.

SOURCE – Takeda.

REFERENCES

1. Nishimoto, T. et al. (Takeda Chemical Industries, Ltd.) *High-density lipoprotein-cholesterol level elevating agent.* JP 2002205956, WO 0238180.

2. Yukimasa, H. et al. (Takeda Chemical Industries, Ltd.) *Benzoxazepine cpds., their production and use as lipid lowering agents.* EP 0862562, EP 1097928, JP 1997136880, JP 2001097963, US 6110909, WO 9710224.

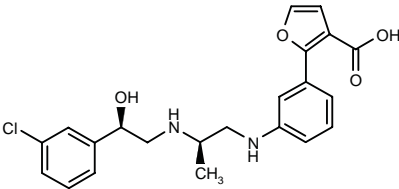
3. Miki, T. et al. *Synthesis of novel 4,1-benzoxazepine derivatives as squalene synthase inhibitors and their inhibition of cholesterol synthesis.* J Med Chem 2002, 45(20): 4571.

4. *IR Meeting.* Takeda Chemical Industries Web Site 2002, May 21.

TREATMENT OF OBESITY AND NUTRITIONAL DISORDERS

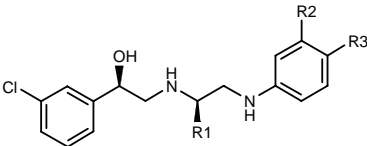
325277

2-[3-[2(R)-[2(R)-(3-Chlorophenyl)-2-hydroxyethylamino]-propylamino]phenyl]furan-3-carboxylic acid



C22 H23 Cl N2 O4; Mol wt: 414.8867

ACTION – β₃-Adrenoceptor agonist expected to be useful for the treatment of obesity and diabetes. Other exemplified compounds include the following:



Compound	R1	R2	R3	Formula
325278	H	3-CO2H-2-furyl	H	C ₂₁ H ₂₁ ClN ₂ O ₄
325280	Me	H	3-CO2H-2-furyl	C ₂₂ H ₂₃ ClN ₂ O ₄
325282	Me	3-CO2H-2-thienyl	H	C ₂₂ H ₂₃ ClN ₂ O ₃ S
325284	H	3-CO2H-2-thienyl	H	C ₂₁ H ₂₁ ClN ₂ O ₃ S
325286	Me	H	3-CO2H-2-thienyl	C ₂₂ H ₂₃ ClN ₂ O ₃ S

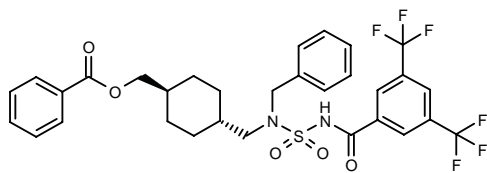
SOURCE – GlaxoSmithKline.

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1. Deaton, D.N. et al. (Glaxo Group Ltd.) *Chemical cpds.* WO 0260885.

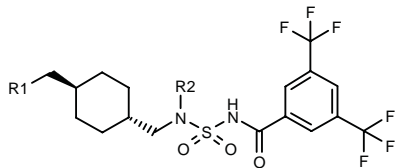
325513

Benzoic acid *trans*-4-[1-benzyl-3-[3,5-bis(trifluoromethyl)-benzoyl]sulfamidomethyl]cyclohexylmethyl ester

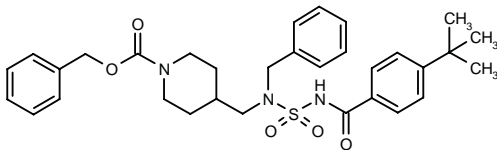


C31 H30 F6 N2 O5 S; Mol wt: 656.6410

ACTION – Potent peroxisome proliferator-activated receptor PPAR γ ligand (antagonist or partial agonist), potentially useful for the treatment of obesity, type 2 diabetes, hyperglycemia and lipid disorders including hypercholesterolemia, hypertriglyceridemia, dyslipidemia and atherosclerosis. Other specifically claimed acyl sulfonamides include the following:



Compound	R1	R2	Formula
325516	OCOBu	CH2Ph	C ₂₉ H ₃₄ F ₆ N ₂ O ₅ S
325518	OCONHPh	H	C ₂₄ H ₂₆ F ₆ N ₃ O ₅ S
325521	OCONHCH2CH2Ph	CH2Ph	C ₃₃ H ₃₅ F ₆ N ₃ O ₅ S
325523	OCONHBu	CH2Ph	C ₂₉ H ₃₅ F ₆ N ₃ O ₅ S
325526	NHCONHPh	CH2Ph	C ₃₁ H ₃₂ F ₆ N ₄ O ₄ S
325528	NHCOPh	CH2Ph	C ₃₁ H ₃₁ F ₆ N ₃ O ₄ S
325529	NHCO2Bu	CH2Ph	C ₂₉ H ₃₅ F ₆ N ₃ O ₅ S
325531	OCONHPh	Et	C ₂₆ H ₂₉ F ₆ N ₃ O ₅ S



325533: C32 H39 N3 O5 S

SOURCE – Merck & Co.

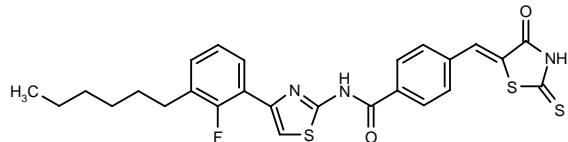
REFERENCES

1. Jones, A.B. and Acton, J.J. III (Merck & Co., Inc.) *Acyl sulfamides for treatment of obesity, diabetes and lipid disorders*. WO 0260388.

HEMATINIC AGENTS AND
HEMATOPOIETIC GROWTH FACTORS

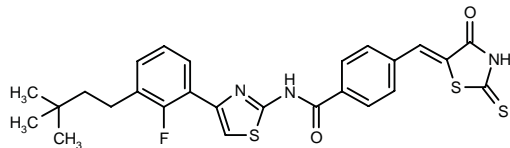
325248

N-[4-(2-Fluoro-3-hexylphenyl)thiazol-2-yl]-4-[(*Z*)-4-oxo-2-thioxothiazolidin-5-ylidenemethyl]benzamide



C26 H24 F N3 O2 S3; Mol wt: 525.6906

ACTION – Thrombopoietin receptor agonist that displayed an EC₅₀ of 0.007 μ M at thrombopoietin receptors expressed in BaF-BO3 cells. Considered to have potential in the treatment of disorders associated with low platelet counts such as thrombocytopenia. Another exemplified compound is:



325249: C26 H24 F N3 O2 S3

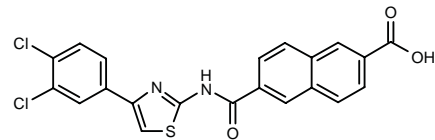
SOURCE – Shionogi.

REFERENCES

1. Takemoto, H. et al. (Shionogi & Co. Ltd.) *Halogen cpds. having thrombopoietin receptor agonism*. WO 0259100.

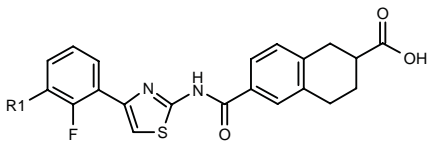
325255

6-[*N*-[4-(3,4-Dichlorophenyl)thiazol-2-yl]carbamoyl]-naphthalene-2-carboxylic acid



C21 H12 Cl2 N2 O3 S; Mol wt: 443.3088

ACTION – Thrombopoietin receptor agonist that displayed an EC₅₀ of 0.023 μ M at thrombopoietin receptors expressed in BaF-BO3 cells. Potentially useful for the treatment of disorders associated with low platelet counts such as thrombocytopenia. Other exemplified cyclic compounds are:



Compound	R1	Formula
325256	F	C ₂₁ H ₁₆ F ₂ N ₂ O ₃ S
325257	C7H15	C ₂₈ H ₃₁ FN ₂ O ₃ S
325258	C8H17	C ₂₉ H ₃₃ FN ₂ O ₃ S
325259	C10H21	C ₃₁ H ₃₇ FN ₂ O ₃ S

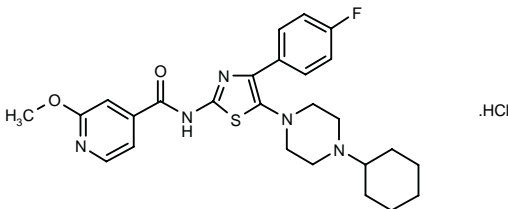
SOURCE – Shionogi.

REFERENCES

1. Takemoto, H. et al. (Shionogi & Co. Ltd.) *Cyclic cpds. having thrombopoietin receptor agonism*. WO 0259099.

326095

N-[5-(4-Cyclohexylpiperazin-1-yl)-4-(4-fluorophenyl)-thiazol-2-yl]-2-methoxypyridin-4-carboxamide hydrochloride



C26 H30 F N5 O2 S . HCl; Mol wt: 532.0809

ACTION – A representative compound from a series of 2-(acylamino)thiazole derivatives with the ability to accelerate megakaryocyte colony formation and therefore increase platelet activity. Potentially useful for the treatment of hypoplastic anemia and thrombocytopenia associated with myelodysplastic syndrome, cancer chemotherapy and radiotherapy, hepatopathy or HIV infection.

SOURCE – Yamanouchi.

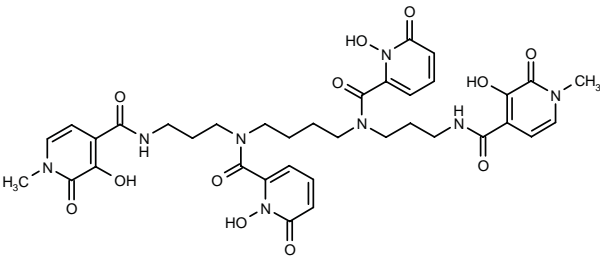
REFERENCES

1. Koshio, H. et al. (Yamanouchi Pharmaceutical Co., Ltd.) *2-Acylaminothiazole deriv. or its salt*. WO 0262775.

TREATMENT OF POISONING,
DRUG ABUSE AND DEPENDENCY

324499

N,N'-(1,4-Butylene)bis[N-(1-hydroxy-6-oxo-1,6-dihydropyridin-2-ylcarbonyl)imino]bis(1,3-propylene)bis(3-hydroxy-1-methyl-2-oxo-1,2-dihydropyridine-4-carboxamide)



C36 H42 N8 O12; Mol wt: 778.7718

ACTION – Metal chelating agent able to remove plutonium from mouse tissues including skeleton, liver, kidneys and soft tissue at doses of 0.03-30 µmol/kg i.p. or p.o. No detectable signs of acute toxicity were seen at a dose of 30 µmol/kg i.p. in mice.

SOURCE – University of California, Berkeley, CA (US).

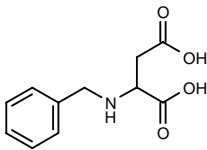
REFERENCES

1. Xu, J. et al. *Synthesis and initial evaluation for in vivo chelation of Pu(IV) of a mixed octadentate spermine-based ligand containing 4-carbamoyl-3-hydroxy-1-methyl-2(1H)-pyridinone and 6-carbamoyl-1-hydroxy-2(1H)-pyridinone*. J Med Chem 2002, 45(18): 3963.

IEM-1770

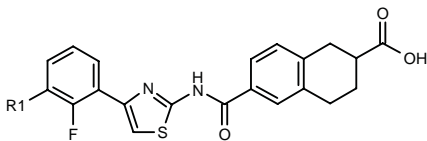
325908

N-Benzyl-DL-aspartic acid



C11 H13 N O4; Mol wt: 223.2267

ACTION – An excitatory amino acid analogue with NMDA receptor-agonist activity, able to prevent the development of alcohol abstinence syndrome (AAS) in rats. In ethanol-preferring rats with free access to ethanol and water over a period of 3 months, compound (30 mg/kg/day i.p.) prevented ethanol-induced severe behavioral deficits including increased immobility in the forced swimming test, reduced motor activity in the open-field test, increased anxiety in the elevated plus-maze test and weight loss. Ethanol intake in animals subsequently given free access to ethanol was also similarly reduced with compound. Potentially useful for the treatment of alcohol dependency.



Compound	R1	Formula
325256	F	C ₂₁ H ₁₆ F ₂ N ₂ O ₃ S
325257	C7H15	C ₂₈ H ₃₁ FN ₂ O ₃ S
325258	C8H17	C ₂₉ H ₃₃ FN ₂ O ₃ S
325259	C10H21	C ₃₁ H ₃₇ FN ₂ O ₃ S

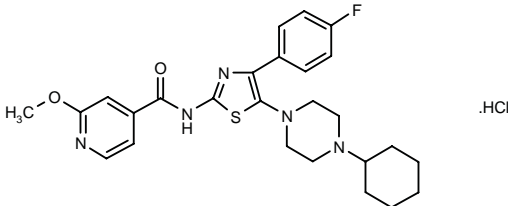
SOURCE – Shionogi.

REFERENCES

1. Takemoto, H. et al. (Shionogi & Co. Ltd.) *Cyclic cpds. having thrombopoietin receptor agonism*. WO 0259099.

326095

N-[5-(4-Cyclohexylpiperazin-1-yl)-4-(4-fluorophenyl)-thiazol-2-yl]-2-methoxypyridin-4-carboxamide hydrochloride



C26 H30 F N5 O2 S . HCl; Mol wt: 532.0809

ACTION – A representative compound from a series of 2-(acylamino)thiazole derivatives with the ability to accelerate megakaryocyte colony formation and therefore increase platelet activity. Potentially useful for the treatment of hypoplastic anemia and thrombocytopenia associated with myelodysplastic syndrome, cancer chemotherapy and radiotherapy, hepatopathy or HIV infection.

SOURCE – Yamanouchi.

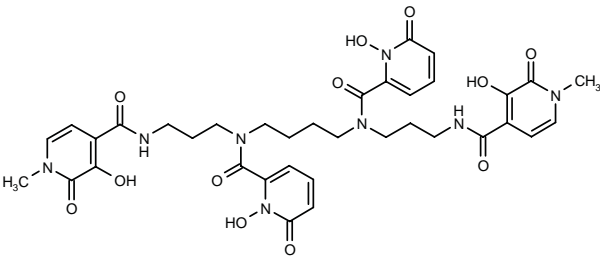
REFERENCES

1. Koshio, H. et al. (Yamanouchi Pharmaceutical Co., Ltd.) *2-Acylaminothiazole deriv. or its salt*. WO 0262775.

TREATMENT OF POISONING,
DRUG ABUSE AND DEPENDENCY

324499

N,N'-(1,4-Butylene)bis[N-(1-hydroxy-6-oxo-1,6-dihydropyridin-2-ylcarbonyl)imino]bis(1,3-propylene)bis(3-hydroxy-1-methyl-2-oxo-1,2-dihydropyridine-4-carboxamide)



C36 H42 N8 O12; Mol wt: 778.7718

ACTION – Metal chelating agent able to remove plutonium from mouse tissues including skeleton, liver, kidneys and soft tissue at doses of 0.03-30 µmol/kg i.p. or p.o. No detectable signs of acute toxicity were seen at a dose of 30 µmol/kg i.p. in mice.

SOURCE – University of California, Berkeley, CA (US).

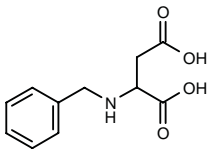
REFERENCES

1. Xu, J. et al. *Synthesis and initial evaluation for in vivo chelation of Pu(IV) of a mixed octadentate spermine-based ligand containing 4-carbamoyl-3-hydroxy-1-methyl-2(1H)-pyridinone and 6-carbamoyl-1-hydroxy-2(1H)-pyridinone*. J Med Chem 2002, 45(18): 3963.

IEM-1770

325908

N-Benzyl-DL-aspartic acid



C11 H13 N O4; Mol wt: 223.2267

ACTION – An excitatory amino acid analogue with NMDA receptor-agonist activity, able to prevent the development of alcohol abstinence syndrome (AAS) in rats. In ethanol-preferring rats with free access to ethanol and water over a period of 3 months, compound (30 mg/kg/day i.p.) prevented ethanol-induced severe behavioral deficits including increased immobility in the forced swimming test, reduced motor activity in the open-field test, increased anxiety in the elevated plus-maze test and weight loss. Ethanol intake in animals subsequently given free access to ethanol was also similarly reduced with compound. Potentially useful for the treatment of alcohol dependency.

SOURCE – Volgograd Medical Academy, Volgograd (RU).

REFERENCES

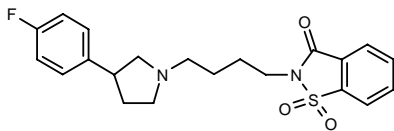
1. Parshev, V. et al. *New analogue of excitatory amino acids IEM-1770 blocks an AAS development in chronic voluntary alcohol drinking rats.* Eur Neuropsychopharmacol 2002, 12(Suppl. 3): Abst P.5.028.
2. Petrov, V.I. et al. *Antidepressant activity of aspartic acid derivatives.* Bull Exp Biol Med 2001, 131(4): 342.

PHARMACOLOGICAL TOOLS

LB-50053*

277033

2-[4-[3-(4-Fluorophenyl)pyrrolidin-1-yl]butyl]-1 *H*-benzisothiazol-3(2*H*)-one 1,1-dioxide



C21 H23 F N2 O3 S; Mol wt: 402.4877

ACTION – High-affinity ligand for 5-HT_{1A} receptors (K_i = 4.2 nM) with strong selectivity over 5-HT_{2A} receptors (K_i = 367 nM), dopamine D2 and D1 receptors (K_i = 263 and > 1000 nM, respectively) and α_2 -adrenoceptors (K_i = 334 nM). In functional studies in *Xenopus* oocytes expressing 5-HT_{1A} receptors coupled to the G-protein-activated inward rectifying K⁺ channel 1 (GIRK1), compound evoked an inward K⁺ current in a manner consistent with partial agonist activity (K_d = 64.6 nM). Potentially useful as a pharmaceutical tool for studies on the 5-HT_{1A} receptor, and also for the treatment of anxiety and depression.

SOURCE – LG Chem Investment.

REFERENCES

1. Ahn, K.H. et al. *N-Substituted-3-arylpyrrolidines: Potent and selective ligands at serotonin 1A receptor.* Bioorg Med Chem Lett 1999, 9(10): 1379.
2. Kim, H.-S. et al. *LB50053: A 5-hydroxytryptamine 1A agent with a high binding affinity and a potency evoking a K⁺ current.* Pharmacology 2002, 65(4): 175.

*Identified compound **277033** (see **277032**) Drug Data Rep 1999, 021(07): 0580.

SOURCE – Volgograd Medical Academy, Volgograd (RU).

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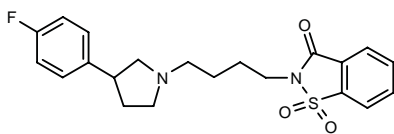
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